SEP 24 1927

VOL. 4 NUMBER 3

ARCHIVES OF PATHOLOGY

AND

LABORATORY MEDICINE

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SEPTEMBER, 1927

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $6.00

Entered as Second-Class Matter, July 30, 1926, at the Postoffice at Chicago, Illinois, Under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Sec. 1103 of Feb. 28, 1925, authorized July 30, 1926.

ARCHIVES OF PATHOLOGY
AND
LABORATORY MEDICINE

VOLUME 4 SEPTEMBER, 1927 NUMBER 3

EARLY INFLAMMATORY REACTIONS IN TISSUES FOLLOWING SIMPLE INJURY*

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The clinical picture of inflammation, as taught by Celsus, has been gradually transformed into a biologic concept which considers inflammation as being a part of almost every disease process. It is a defense reaction which is more or less uniform throughout the whole animal kingdom. The local response to an injury results in an alteration in morphology with vascular, cellular and tissue fluid changes, which in turn give rise to the clinical signs of swelling, heat, redness, pain and loss of function.

The stimulus that calls forth an inflammatory response may be living organisms or any physical or chemical agent that will damage tissue cells. The simplest type of injury that can be produced is the mechanical disruption of living cells, as, for example, cutting living tissue with a sharp knife.

Alteration in tissue morphology is the earliest indication of the onset of an inflammatory reaction. The introduction of the microscope and histologic methods of study changes the criteria for an inflammatory reaction from the simple macroscopic signs to the minute changes observed in inflammatory hyperemia and exudation of serum and cells. Particular stress has been placed on the migration of leukocytes from the blood vessels into the fixed tissues of the affected part. The vascular changes preceding this migration have been well studied in the living tissues under the microscope. In histologic sections, the vascular changes are not as apparent, so more reliance has been placed on the reaction of the leukocytes.

Most authors, in their descriptions of the inflammatory reactions, describe those that occur several hours after the action of the inciting cause, or in a general way indicate that the process is gradually progressive without stating specifically when the onset may be recognized. This is particularly true in the descriptions of the first appearance of a reaction following a simple injury. There the stimulus is believed to be

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so slight that the reaction is slow in starting, and it is never significant. In the reactions following other stimuli, such as bacterial infection or chemical and physical irritants, the response may be more marked, and these have received most attention in the literature. John Hunter [1] was the first to make accurate observations on the earliest appearance of an inflammatory reaction. He associated this condition with changes in the vessels, and he described a dilatation of the blood vessels occurring almost immediately subsequent to the production of an injury. However, he thought that these vascular changes preceded the true inflammatory reaction. He also found what he describes as "pus globules" at the end of twenty minutes after the production of a simple injury. Hunter believed that pus came from the blood, but he failed to realize the significance of these pus globules.

Dutrochet,[2] in 1842, and Addison,[3] Gulliver [4] and Barry,[4] in 1843, were the first to affirm that pus cells and white blood cells were the same. This opinion was confirmed by Waller [5] in 1846. He used the method later employed by Cohnheim [6] and described the active passage of leukocytes through the vessel wall and their collection in the surrounding tissue. Previously, in 1841, Williams [7] had described the margination and collection of the leukocytes along the vessel walls. Recklinghausen [8] was one of the first to call attention to the similarity of the ameboid movements of the pus cells and the leukocytes.

Jones,[9] in 1850, and Lister,[10] in 1858, both described the clumping of the leukocytes in the small capillaries; both noted that the vascular changes occurred quickly following an injury, but neither grasped the importance of Waller's work. Virchow [11] also failed to appreciate the significance of the leukocytes, although he mentions the opinions of Addison and Zimmermann that they were interchangeable with the pus cells.

It remained for Cohnheim in 1872 to establish fully the rôle played by the leukocytes in inflammation, and to put the earlier work of

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1. Hunter: Treatise on Blood, Inflammation and Gun Shot Wounds, Philadelphia, Hasswell, Barrington and Hasswell, 1792.
2. Dutrochet, cited by Ziegler (footnote 32).
3. Addison: Tr. Prov. M. & S. A., London **11**:233, 1843.
4. Cited by Addison (footnote 3).
5. Waller: Phil. Mag., series III **29**:271 and 397, 1846.
6. Cohnheim: Lectures on General Pathology, transl., London, New Sydenham Society, 1899.
7. Williams, cited by Lister (footnote 10).
8. Recklinghausen, cited by Councilman: Dennis' System of Surgery, Philadelphia, Lea & Febiger, 1895, vol. 1, p. 145.
9. Jones: Guy's Hosp. Rep., series II **7**:1, 1850-1851.
10. Lister: Phil. Tr. Roy. Soc. **148**:645, 1858.
11. Virchow: Cellular Pathology, transl., New York, R. M. DeWitt, 1858.

Addison and Waller on a firm basis. Accordingly, he is usually given the whole credit for the basic principles underlying inflammation, although he thought the leukocytes were passively forced through openings in the capillary walls by pressure from within. This emigration of the white blood cells, he pointed out, might take place quickly, or take one hour or more, but after a period of five or six hours the vessels had a definite layer of white blood cells outside them.

The dilatation of the blood vessels, slowing of the blood stream and stasis which Cohnheim described so accurately and which he said may take place within from fifteen to twenty minutes in the frog, had been previously described by several English authors: Williams, Addison, Waller, Jones and Lister. All these experimenters found that in the frog these reactions occurred within one hour.

Using similar methods of direct microscopic observation of transparent tissues of various animals, other more recent authors have confirmed the observations of the earlier investigators both as to the different phases of the reaction and also as to its early appearance (Ikeda,[12] Ricker and Regendanz,[13] Wolf,[14] Bloom,[15] Wood[16] and others). Indeed, Rich[17] has shown that the dilatation of the capillaries following exposure and handling of the mesentery of a cat occurs almost immediately, within one and one-half minutes.

Metchnikoff[18] demonstrated the presence of protective phagocytic cells in invertebrates, and in tadpoles, at the end of three quarters of an hour after an injury, he found an increased number of motile phagocytes in the affected part.

Durham[19] found that in guinea-pigs killed eight minutes after an injection of 1 cc. of peptone broth, the capillaries of the mesentery were completely blocked with leukocytes, and even at this early stage a few had begun to traverse the walls of the small vessels. In animals killed from fifteen to thirty minutes after injection, active emigration was constant. Sollmann[20] quotes Gilchrist's statement that this occurs within fifteen minutes in urticarial wheals.

The reaction following the introduction of bacteria has been commonly studied in histologic sections or by noting the first increase in

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12. Ikeda: J. Pharmacol. & Exper. Therap. **8**:101 and 137, 1916.
13. Ricker and Regendanz: Virchows Arch. f. path. Anat. **231**:1, 1921.
14. Wolf: J. Exper. Med. **37**:511, 1923; **34**:375, 1921.
15. Bloom: Bull. Johns Hopkins Hosp. **33**:185, 1922.
16. Wood, in Delafield and Prudden: Text Book of Pathology, New York, William Wood & Company, 1925, p. 97; and in Keen: System of Surgery, Philadelphia, W. B. Saunders Company, 1912, vol. 1, p. 348.
17. Rich: J. Exper. Med. **33**:287, 1921.
18. Metchnikoff: Lectures on Comparative Pathology, transl., London, Regan, Paul, French, Trübner & Co., 1893.
19. Durham: J. Path. **4**:368, 1897.
20. Sollmann: J. Pharmacol. & Exper. Therap. **9**:309, 1917.

cell content of the fluid of serous sacs. Opie [21] noted that when bacteria and inanimate particles were injected into the peritoneal cavity they passed through the lymph glands, but later, at the end of half an hour, their exit was obstructed, and at this time an inflammatory reaction had begun at the site of injection and within the lymph gland. Furthermore, tubercle bacilli injected into a serous cavity were surrounded and ingested by polymorphonuclear leukocytes within one hour. Gastrich [22] found that living bacteria or their toxins caused an inflammatory reaction within one and one-half hours when injected subcutaneously into white mice. Beattie [23] noted the first increase in cells of the peritoneal fluid of guinea-pigs in from one to two hours after the injection of pathogenic organisms. Muir [24] noted that the first increase in the cells occurred within from two to three hours. Following the introduction of a culture of virulent pyogenic organisms into the tissues of a rabbit, Adami [25] found that four hours elapse before definite inflammatory changes are recognizable. Subcutaneous injections of agar initiated a response in from three to six hours, according to Lang,[26] but Forbes [27] did not note a reaction until eighteen hours had elapsed.

These examples serve to illustrate the diverse estimates of the time of appearance of the initial inflammatory reactions following various types of injury. When one considers the reactions following aseptic wounds, a similar lack of uniformity of opinion is encountered. Cornil and Ranvier [28] and Beattie and Dickson [29] stated that there is an increase in polymorphonuclear leukocytes in the tissues at the edge of a cut after from five to six hours. Wood put the time at eight hours; Woodhead [30] placed it at twelve hours, while Elsberg [31] and Ziegler [32] first noted it at the end of twenty-four hours. This divergence is

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21. Opie, E. L.: Inflammation, Arch. Int. Med. **5**:541 (June) 1910.

22. Gastrich: Arch. f. klin. Chir. **129**:621, 1924.

23. Beattie: J. Path. **8**:129, 1902.

24. Muir: Text Book of Pathology, Philadelphia, J. B. Lippincott Company, 1924.

25. Adami: Inflammation: An Introduction to the Study of Pathology, New York, The Macmillan Company, 1909.

26. Lang, F. J.: Rôle of Endothelium in the Production of Polyblasts in Inflammation, Arch. Path. **1**:41 (Jan.) 1926.

27. Forbes: J. M. Research **20**:45, 1909.

28. Cornil and Ranvier: Manuel d'histologie pathologique, Paris, Félix Alcan, 1901, p. 206.

29. Beattie and Dickson: Text Book of Pathology, London, William Heinemann, 1926, p. 162.

30. Woodhead: Practical Pathology, New York, Oxford University Press, 1910.

31. Elsberg: J. Exper. Med. **4**:479, 1899.

32. Ziegler: General Pathology, transl., New York, William Wood & Company, 1908.

the result, in part, of the nature of the experiments and, in part, of the fact that the investigators did not study the tissues at an early period.

However, Marchand [33] in his book "Wundheilung" states that an inflammatory state follows quickly the production of clean incised wounds and that a widening of the blood vessels occurs almost immediately. Within three quarters of an hour there is a greater number of polymorphonuclear leukocytes in the neighboring blood vessels, and within one hour there is a greater number of leukocytes outside the blood vessel walls.

Because of the scarcity of observations on the reactions following simple injury in tissues it seemed advisable to do some experimental work on this problem. Accordingly, I performed a series of experiments on rabbits to determine, if possible, the earliest period at which an inflammatory reaction can be recognized by histologic methods.

EXPERIMENTAL METHODS EMPLOYED

Healthy adult female rabbits were anesthetized with ether; under aseptic precautions the abdomen was opened and clean one-half inch incisions were made in the liver, spleen, left kidney and left horn of the uterus. The abdomen was then closed with catgut sutures. At definite periods after the injury, the animals were killed with ether, or by a blow on the neck. The abdomen was quickly opened and the tissues were removed and at once placed in 10 per cent formalin. In some cases the abdominal cavity was quickly flooded with formalin and the organs were removed and placed in other 10 per cent formalin. Control experiments were made by placing incisions in the same or, where possible, in the opposite organs of the same animal at the time of death, and then removing the tissue and fixing it. In other cases the first incisions were made just at the time of death, but instead of removing the tissue the abdomen was closed as in the case of the living animal, and the organs were not removed and fixed until half an hour or one hour after the death of the rabbit. Again, in other instances, instead of closing the abdomen of the dead animal a warm moist towel was laid over the abdominal opening and incisions were made ten minutes and half an hour after death and the tissues were not removed for another half hour. In this manner incisions were obtained which were left for time periods varying by half hour intervals from one hour after death to three hours after infliction in the living animal. In this series the organs were the liver, spleen, kidney and uterus.

Incisions in the liver were made at ten minute intervals up to one hour in a living animal. Wounds also were made in the ear at fifteen minute intervals up to one hour. The ear was then clamped off,

33. Marchand: Wundheilung, Stuttgart, Ferdinand Enke, 1901.

removed and fixed. Cuts made in the other ear after its removal served as controls.

All of the foregoing experiments were repeated on a number of animals, and comparison was made with preceding observations. Some quantitative variation in the reaction was found in each group, but the general characters were the same.

The tissue around the wounds after fixation in 10 per cent formalin for from two to three hours was divided, and half of it was then put in Zenker's fluid for twenty-four hours. The remaining half was left in the formalin. Blocks of this tissue were embedded in paraffin, and sections 4 microns thick were cut. The staining methods employed were hematoxylin and eosin, phosphotungstic acid hematoxylin and occasionally van Gieson's and Wright's (eosin-methylene blue).

ANALYSIS OF RESULTS OF EXPERIMENTS

In general the reaction was found to be gradually progressive, starting immediately on the production of the injury. The reaction was more pronounced in the liver than in the other organs, and accordingly this will be described first.

Following an incision there was a short period of free hemorrhage, and in some cases light and dark streaks were seen in the blood flowing from the open wound. The bleeding ceased in from one to one and a half minutes. The cut margins fell together and were cemented by strands of fibrin. The incisions, which were removed and fixed as soon as possible after their production, showed that already the formation of fibrin had commenced. The time elapsing between the production of the cut and the dropping of the tissue in formalin in no case was longer than three minutes and in most instances was less than one minute. The fibrin was in the form of fine, threadlike strands, closely related to the injured cells along the margin of the wound, and sometimes was seen as small, radiating, bushy masses attached to a damaged cell. The fibrin formed first at the sides of the incision. Frequently, it was found that some of the red cells in the center of the wound gap had fallen out, leaving the first threads of fibrin attached to the layer of injured cells.

The cells that were damaged by the passage of the knife stood out prominently. Their cytoplasmic granules were swollen and took a deeper eosin stain than normal. Their nuclei also stained more deeply whether fragmented by the knife or left intact.

The leukocytes in the blood that flowed from the opened sinusoids were regularly distributed through the mass of red cells, but most of them were enmeshed in the fibrin layer immediately adjacent to the sides of the wound. Furthermore, they showed a tendency to form small clumps; this was still more pronounced in the later periods.

Half Hour Period.—In the wound area removed in half an hour, these changes were more marked. Interlacing strands of fibrin were then more dense and numerous, reached from one cut margin to the other and held in their meshes the red and white blood cells. The margination and clumping of the leukocytes were then more noticeable, and here and there, in close contact with the liver cells, were clusters of three or four polymorphonuclear leukocytes. The mononuclear cells (endothelial cells) were especially close to the injured liver cells. Their cytoplasm appeared to have flown out over the cut surface of the hepatic cells and their nuclei were parallel to the margin of the cut. This appearance made it difficult in some cases to distinguish between the nucleus of an endothelial cell and early pyknotic changes in a liver cell. In many places the open sinusoids were partly filled with leukocytes, and for a short distance from the edge of the wound the sinusoids contained a greater number of white cells than did the surrounding normal tissue.

At the bottom of the cut and for some distance laterally, the liver cords were distorted and showed evidences of cell injury. Apparently, the downward pressure of the knife transmitted a disruptive force for some little distance in the direction of its action. At the bottom of the cut were also small masses of fragmented nuclei which at first glance somewhat resembled clumps of bacteria. The collection of leukocytes was most marked at the bottom of the incision.

To a certain extent the degree of reaction varied with the amount of injury. In certain cases the incision was irrigated with a saline solution until the bleeding ceased. This occurred in from ten to twelve minutes. In these cases, the liver cells for a considerable distance from the edge of the incision were swollen, took a deeper eosin stain and showed early pyknosis. The sinusoids between these cells were packed with leukocytes, and fibrin had formed in the sinusoids for some distance from the side of the wound.

One Hour Period.—The same changes were seen in the wound areas removed after the one hour period as after the half hour, but they were more marked. The injured cells had begun to disintegrate. Their nuclei were small and deeply stained, while the cytoplasm was broken up. The total number of white cells within the incision was much greater than in the half hour period, and the clumps of leukocytes contained from five to eight cells.

One and One-Half Hour Period.—In sections representative of this period it was difficult to make out the outline of the damaged cells. They seemed to be completely disintegrated into a pink staining, finely granular fringe of débris along the edge of the incision. Along the sides of the wound mixed with this cellular débris were clumps of leukocytes numbering from ten to twelve cells each. One case showed

clumps of almost similar size some distance from the cut margin. With the phosphotungstic acid stain the fringe of cellular débris stood out prominently as a deep blue layer lining the sides of the wound.

Two Hour Period.—After two hours there was not any sign of the injured liver cells. In little pocket-like depressions corresponding to the position previously occupied by these cells, groups and masses of leukocytes were seen.

Two and One-Half Hour Period.—One of the blocks removed at this time period showed an incision with its edges tightly cemented. The depth of the wound was ballooned with a serous exudate in which there were interlacing strands of fibrin with many leukocytes along the edges. The cut passed close to a large vein, and the sinusoids between this and the incision and for some distance back from the edges on either side were filled with white cells. This infiltration of cells was the most marked example yet noted. The fibrin apparently had not penetrated deeply into these sinusoids.

Three Hour Period.—The reaction about the wound was practically the same as that seen in the two and one-half hour period, save that the leukocytic collection was greater.

The cuts in the liver at ten minute periods up to one hour illustrated nicely the progressive nature of the reaction in this organ.

The wound area removed in ten minutes had more cells per high power field along the margins than the ones removed immediately after injury. At twenty minutes this was still more noticeable, and there was an increase in the number of leukocytes in the sinusoids. The condition at the end of half an hour has already been described. At the end of forty minutes the sinusoids near the edge of the wound were full of leukocytes, while after fifty minutes clumps of polymorphonuclear cells were present in the dilated sinusoids. The reaction at the one hour period also has been described.

This series of incisions is interesting in that the wounds were made in the same organ and hence were not subject to possible variation incident to the use of different animals. With the possible exception of the fifty minute and one hour periods, it was easy to distinguish the difference in reaction that had taken place in each ten minute interval.

Wounds in Spleen.—In the incisions in the spleen bleeding was most profuse for from ten to fifteen minutes and then it gradually lessened, but in most cases considerable oozing occurred half an hour later. In one hour the bleeding usually had ceased, with a firm clot covering the incision. The wounds had a tendency to gape so that in the sections they appeared as wide V-shaped notches filled with clotted blood.

Because of the number of leukocytes normally present in the spleen, it was more difficult to note a quantitative distinction in the reaction in

this organ than in the liver. The incisions which were removed immediately, showed that fibrin was forming along the margins, but the white cells appeared evenly distributed throughout the mass of hemorrhage. After half an hour the number of leukocytes in the wound had markedly increased, and there were more along the edges than in the central part. This tendency to marginate was not as prominent as in the case of the liver. Apparently, the number of leukocytes present was directly proportional to the amount of hemorrhage. Evidently the white cells were more easily entangled in the strands of fibrin so that the majority of them stayed in the wound while the red cells were still able to escape. In the later periods a well established increase took place in the number of the polymorphonuclear leukocytes along the margin of the incision. This tendency first noted in the half hour preparation, was marked in one hour and from this time on steadily increased.

Wounds in Kidney.—The wounds in the kidney bled freely, but the bleeding usually ceased within two minutes. This occurred in spite of the fact that the wounds also tend to gape and the sections made from them contained a large amount of blood clot. As in the liver, the tendency of the leukocytes to marginate was seen in the earliest sections. Fibrin also formed within a few seconds.

At half an hour definite clumps of leukocytes had formed along the margins of the cut. For some distance from the wound, especially toward the bottom and in the direction of the line of incision, the blood vessels between the tubules were much dilated and were filled with red and white blood cells. Many of them near the incision contained an increased number of leukocytes and in one case in which the vessels were cut longitudinally as they opened into the wound, they were packed with polymorphonuclears. At the half hour period the majority of the damaged tubule cells were desquamated into the lumina and showed marked pyknosis and other evidences of degeneration. Wood says that these degenerative changes are first seen at the end of one hour, but in my cases they were definite in half an hour. From this stage on, the reaction is similar to that found in the liver and so need not be described further.

Wounds in Uterus.—Following the incision, the uterus contracted within a few mintues, and its appearance changed from that of a highly vascular organ to that of a blanched anemic one. The bleeding ceased in about two minutes but a certain amount of serous oozing continued for from ten to fifteen minutes. The wound areas removed immediately showed some formation of fibrin but little other change indicative of an inflammatory reaction. The nuclei of the muscle cells damaged by the passage of the knife were smaller and more deeply stained than the others, while the cytoplasm of the fibers was more acidophilic.

At the half hour period the degenerative change in the muscle cells was more marked, but the inflammatory exudate was still slight. That it had begun was evident by the presence of a few polymorphonuclear leukocytes where the incision had just nicked the inner muscular layer, and small groups of leukocytes were noted in and about the distended vessels, and a few red cells and fibrin between the muscle fibers. This collection of leukocytes was more apparent at the end of one hour but was still slight compared with that noted in the liver or kidney. At the end of one and one-half hours the serous exudate was sufficiently great to separate the muscle fibers on either side of the incision, and a few more leukocytes were diffusely infiltrating the area. This serous exudate increased so that by the end of three hours the tissues around the wound were edematous and the infiltration of leukocytes was marked.

Wounds in Subcutaneous Tissue.—A series of incisions was made in the ear to compare the reaction in the skin and subcutaneous tissue with that found in the abdominal organs. The skin of the ear did not retract from the edges of the wound to the same extent as the tissues in other parts of the body and this made it possible to obtain better sections.

Margination of the leukocytes was not present in the incisions removed immediately, and, in fact, few wandering cells were seen in these sections. However, fibrin had begun to form already. At the fifteen minute period the vessels adjacent to the incision were more engorged than was noted in the walls of the wound removed immediately. Some of the free hemorrhage had spread into the tissues surrounding the incisions and separated the connective tissue fibers. After half an hour, the subcutaneous tissue near the incision contained more free hemorrhage than at the fifteen minute interval, and it was slightly edematous. Also, a few more polymorphonuclear leukocytes were present along the margin of the blood vessels. The increase in the number of leukocytes was definite after three quarters of an hour. Some of the capillaries contained small clusters of them closely applied to the vessel wall. Emigration of the leukocytes had also commenced, and some were seen in the tissue spaces near the capillaries. This reaction progressed and was still more marked at the one hour period, but as the main interest was in the earliest appearance of the reaction the time intervals were not prolonged beyond the hour.

Wounds after Death.—The incision made at the time of death of the animal, when the heart had stopped beating, and then removed half an hour or one hour later, showed that death of the organism as a whole and death of tissue are two different events. It was found that although the rabbit was dead the individual tissues still had the power to react to injury. It was obvious that this was not as marked as in the living

animal, but nevertheless it was possible to observe some of the early inflammatory changes, as previously described.

In an incision into the liver, fibrin was found in and about the wound to an almost equal degree. A greater number of leukocytes was found in the sinusoids adjacent to the cut than in the neighboring tissue, and they showed the same margination and tendency to clump close to the damaged liver cells. An incision made ten minutes after death and then left for half an hour showed less reaction than the one made just at death. One made half an hour after death and left for a further half hour did not show any inflammatory change. Yet the wound made at death and left for one hour had a greater reaction on the part of the leukocytes than one made at death and left only half an hour. The reaction in the other tissues examined (spleen and kidney) was similar to that in the liver, while in the uterus and the subcutaneous tissue the change was less.

The circulation of the blood in the smaller ramifications of the vascular tree did not stop immediately when the heart stopped beating. A liver incision irrigated with saline solution to prevent massive formation of fibrin will bleed for ten minutes. A rapid circulation was also seen in the capillaries of a rabbit's lower eyelid, which was removed ten minutes after the heart had stopped beating. Other observers have also noticed this postmortem circulation in the capillaries, and recently Magnus [34] showed that a circulation was maintained in the gallbladder, and in hydrocele and hernial sacs for from fifteen to twenty minutes after they were removed. This circulation consisted of an emptying of the arterial side of the vascular system into the more easily distensible venules and longer veins. The larger arterioles emptied first, then the smaller arterioles and finally the arterial half of the capillary loop. Magnus found that the circulation was not dependent on gravity and that it appeared to be due to the inherent contractility of the arterioles. Furthermore, he found that injury to an area in these tissues caused a normal local capillary dilatation and redistribution of the blood to give a greater supply to the affected part.

That the leukocytes are still capable of movement for some time after the death of the person is well known. Waller described emigration of leukocytes through the vessel walls occurring after death. Metchnikoff also saw leukocytes passing through the walls of vessels after the heart stopped beating. The interesting work of Lewis [35] and Sabin [36] on tissue culture growth and vital staining of leukocytes also shows that they retain their vitality for a considerable time.

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34. Magnus: Arch. f. klin. Chir. **120**:96, 1922.

35. Lewis: Am. J. Path. **1**:91, 1925.

36. Sabin: Bull. Johns Hopkins Hosp. **34**:277, 1923.

COMMENT

These observations illustrate the perfect balance which exists between the component parts of a living organism. When this balance is upset the body reacts quickly. This early reaction has already been noted in the rapid margination of the leukocytes along the sides of the incisions over which the hemorrhage is flowing. This is a physical phenomenon which is apparent. It is logical to suppose that changes of a chemical nature not to be detected by histologic methods have preceded the redistribution of the leukocytes. What physiochemic change takes place immediately after the rupture of a cell membrane by the knife is hard to say, and it is not my intention to enter into any theoretical discussion of the part played by the liberated colloids and protein molecules. Rous and Drury [37] have shown that when a cell is injured a change takes place quickly in the intracellular hydrogen ion concentration. What relationship does this alteration bear to the migration of leukocytes?

The subject of chemiotaxis is so involved and the literature is so extensive that an adequate discussion of the problem is material for a paper by itself. For this reason and because of lack of any new facts relative to the actual phenomena, it is not necessary to go into too great detail. Wells [38] notes that tissue proteins that are altered in necrosis are chemiotactic as also are extracts of tissues. This is a fact that has been well established. With reference to the mode of action of these chemiotactic substances he says that at the very least the surface tension explanation of leukocytic action agrees perfectly with most of the observed actions of leukocytes. However, he does not believe it to be the full explanation.

With the interesting work of Rous [39] in mind, I performed some experiments to demonstrate if possible the relationship between the change in hydrogen ion concentration, and the leukocytic response. It was thought that probably the initial margination of the leukocytes was partly due to a difference in electric potential between the leukocytes and the damaged cells. That this difference in potential, if it really exists, should affect the white blood cells more than the red cells is hard to understand, and yet Abramson [40] found that when blood cells in vitro are subjected to a constant direct current the lymphocytes flow toward the anode at an average rate of 15 microns per minute.

It has long been known that injured tissue is electrically negative to the surrounding normal tissue. This is indicated by connecting one pole of a sensitive galvanometer to the injured cells and the other pole

37. Rous, Peyton, and Drury, D. R.: Outlying Acidosis, J. A. M. A. **85**:33 (July 4) 1925.

38. Wells: Chemical Pathology, ed. 4, Philadelphia, W. B. Saunders Company, 1920, p. 247.

39. Rous, Peyton: J. Exper. Med. **41**:379, 399, 451 and 739, 1925.

40. Abramson: Am. J. M. Sc. **167**:702, 1924.

to the normal tissue and noting the direction of the current by the deflection of the galvanometer needle. The white blood cells being in a fluid medium will easily move in the direction of the electrical current, and, as Abramson found in his in vitro experiments, this will be toward the anode. The increase in positive charge making the injured cells the anode is probably due to the local increase in hydrogen ions, and so the change in p_H should bear some relationship to the early inflammatory response.

Rabbits, guinea-pigs and white mice were injected with the phenol-sulphonphthalein indicators used by Rous, but the interpretation of the p_H reactions varied so greatly that I could not place any reliance on the method, and the results from my standpoint were entirely negative.

I next tried to evolve an electrometric method for determining whether any change occurred in the p_H of the small amount of serous exudate which came away from the wounds. A small vessel with an electrode somewhat similar to that devised by Bodine and Fink [41] was constructed, but here again the application of it to my problem was unsatisfactory, and this method was given up.

Equally unsuccessful was another manner of approach. This was a modification of a method used by Wolf in her work on the chemiotactic effect of various substances on the leukocytes. A series of agar molds having different p_H values was made, and freshly drawn rabbit's blood was placed in V-shaped incisions in these; the preparations were incubated for half hour and one hour periods. Paraffin sections were then made and cut, stained and examined to see whether the leukocytes showed any tendency to marginate to the edges of the cut. No appreciable difference was observed in the distribution of the leukocytes at any of the p_H values tested.

Another factor that may help explain the early collection of the leukocytes along the cut edges has already been suggested. It is here that the fibrin first starts to form, and it is probable that the leukocytes are caught in their strands and so arrested along the cut edges. However, this does not explain the tendency of these leukocytes to clump together. This attraction of one leukocyte for another was frequently commented on by the early workers on inflammation. Lister also noted that the red cells tended to adhere one to another as if they were "sticky." Woolley [42] explains this adhesiveness of the red and white cells as due to the effect of acid radicles on protein molecules and on intracellular colloids. He attributes the slowing of the blood stream to similar changes in the endothelial cells and blood cells as well as an increased viscosity of the fluid part of the blood.

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41. Bodine and Fink: J. Gen. Physiol. **7**:735, 1925.

42. Woolley, P. G.: Factors Governing Vascular Dilatation and Slowing of the Blood Stream in Inflammation, J. A. M. A. **63**:2279 (Dec. 26) 1914.

It is possible that the sequence of events is, therefore, somewhat as follows: The passage of the knife through living cells such as those of the liver cords leads to an immediate physical and chemical change in their contents with the rapid production of acids, an increase in hydrogen ions and the collection of positive electrical charges. The difference in potential between the injured cells and the leukocytes then probably starts them moving toward the margin of the incision. The acids tend to raise the viscosity of the outflowing blood immediately adjacent to the injured cells and at the same time tend to affect the leukocytes in such a way as to make them adhere to substances more readily by lowering their surface tension. At the same time that this is occurring fibrin is being formed along the edges of the injured cells and also serves to slow down the blood stream flowing past. The white cells are more easily caught in the fibrin strands because of their lowered surface tension, while the fibrin forms a scaffolding for them to travel toward the injured cells. It has already been shown that these changes take place quickly.

It has been noted that there is a quantitative difference in the degree of reaction in the organs studied. This would appear to bear a direct relationship to the number of cells destroyed or damaged. In highly specialized tissues such as those of the liver and kidney where cells are relatively rich in cytoplasm, the inflammatory response is much greater than in spleen, uterus and subcutaneous tissue. In the liver the response was directly proportional to the amount of damage on the liver cells. This relationship between the number of cells injured and the degree of response is illustrated in another way. A light scratch on the surface of the liver, spleen or kidney is followed almost immediately by a livid streak of dilated surface vessels, yet sections removed from this area in half an hour show but slight alteration. However, if an incision is made with a hot razor blade in the same organs, the cells show signs of injury for 2 or 3 mm. from the edge of the wound, and in half an hour the inflammatory reaction is marked. A somewhat similar effect was also noted in the liver incisions that were washed with saline.

Various attempts have been made to isolate from injured tissue chemical substances that will induce an inflammatory reaction, and it has been found that histamine, injected intravenously or applied locally, will produce changes in the capillaries characteristic of an inflammatory response (Dale,[43] Laidlaw,[44] Richards,[45] Rich, Leo Loeb [46] and others).

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43. Dale: Brit. M. J. **1**:959 and 1006, 1923.

44. Dale and Laidlaw: J. Physiol. **52**:355, 1919.

45. Dale and Richards: J. Physiol. **52**:110, 1918.

46. Loeb: Oedema, Medicine Monographs, Baltimore, Williams & Wilkins Company, 1923, vol. 3.

Bloom did not believe that histamine exerted any chemiotactic effect on the leukocytes when it was introduced into the subcutaneous tissue by means of collodion capsules or capillary tubes. Wolf, using a different method, found that local application of histamine did cause an emigration of leukocytes. Just what rôle histamine plays in inflammatory reactions is not certain, but it is possible that the cell injured leads to the production of it or allied substances, and that they act as capillary poisons causing dilatation and increased permeability of the capillary walls, which in turn allow the escape of the fluid and cellular contents. The production of such toxic substances would obviously run parallel with the number of cells injured.

The blood supply to an organ also assists in determining the extent of the tissue reaction. Thus it is noted that following an incision in the uterus, the organ quickly blanches through muscular contraction and little bleeding takes place. Consequently, relatively fewer white cells are found about the incisions in the uterus than in those of the spleen. The latter organ illustrates the other extreme. Here the hemorrhage is profuse and prolonged. This serves to bring a large number of white cells to the wounded area and, although many escape, more are found within the confines of the incision than in the kidney or liver. The spleen appears to be somewhat deficient in the exciting factor, for the leukocytes there do not possess the same tendency to cluster along the margins of the incision as they do in the liver or kidney. In the latter, although there was some variation in the bleeding time as well as in the amount of reaction after the same time intervals, it was not possible to link up these two factors in a logical sequence.

The action of the nervous system in inflammation has received the attention of investigators from the earliest days, although my work did not lend itself to a study of its effect. Yet the recent observations of Mueller [47] are worthy of notice. He describes a redistribution of the leukocytes of the body after the intravenous injection of peptone solution or the intracutaneous injection of various nonspecific albuminous preparations, salt solution, distilled water and even air. Within a space of fifteen minutes there was a marked leukopenia in the vessels of the skin, and the leukocytes were collected in the splanchnic areas. Mueller believed this was due to a disturbance of the sympathetic and the parasympathetic nervous systems. In a few instances blood counts were made from the peripheral circulation and from the splanchnic area at frequent intervals during the course of the experiment, and my results tend to bear out Mueller's assertion of the occurrence of a redistribution of the leukocytes. In one case the white count from a rabbit's ear before the anesthetic was 7,500. Fifteen

47. Mueller, E. F.: Evidence of Nervous Control of Leukocytic Activity by Involuntary Nervous System, Arch. Int. Med. **37**:268 (Feb.) 1926.

minutes later, when the animal was over the stage of excitement of anesthesia, the count from the vein in the ear had risen to 17,000. A few minutes later blood obtained from a cut in the liver had a count of 10,200, while just preceding this the peripheral count had fallen to 14,800. An hour and a half later the blood count of the liver had fallen to 7,700, owing, without doubt, to hemorrhage from the incisions in the other organs, but the count of peripheral blood was now only 4,000. The number of leukocytes in the splanchnic part of the circulation fell from 10,200 to 7,700, while that in the peripheral circulation fell from 14,800 to 4,000.

The initial rise in the leukocyte count of the blood drawn from the ear was no doubt associated with the emotional disturbance that the animal experienced in being anesthetized. Similar observations on the effect of emotional disturbance on the leukocyte count have recently been reported by Mora, Amtman and Hoffmann.[48] The relative increase in the leukocytes of the visceral circulation over that in the peripheral circulation, as noted in my experiments, appears to be associated with the injury to the abdominal organs.

However, the significance and mode of action of the autonomic nervous system on the distribution of the leukocytes in the vascular system will require further study before its relation to an inflammatory reaction can be fully understood.

The reactions occurring in tissues immediately after the death of the animal are interesting in that it is commonly thought that none take place. Yet medicolegal authorities have frequently mentioned the difficulty of distinguishing a wound made a short time preceding death from one made just after death. Balch and Lewis [49] say that a wound made immediately after death or within half an hour may resemble closely one made before death. My observations on the histologic appearances of wounds tend to bear out these naked eye observations. It was practically impossible to distinguish between a wound made a few minutes before death in the tissues studied and one made immediately after death.

However, in all of my cases, a wound made as late as half an hour before death showed a greater inflammatory response than any made at or just after death.

SUMMARY

1. A reaction definitely inflammatory in character rapidly takes place in tissues following aseptic incisions.

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48. Mora, J. M.; Amtman, L. E., and Hoffman, S. J.: Effect of Mental and Emotional States on Leukocyte Count, Evidence of Nervous Control of Leukocytic Activity by the Involuntary Nervous System, J. A. M. A. **86**:945 (March 27) 1926.

49. Balch and Lewis, in Peterson, Haines and Webster: Legal Medicine and Toxicology, Philadelphia, W. B. Saunders Company, 1923, vol. 1, p. 286.

2. The earliest stages of this reaction can be recognized by histologic methods, and in all tissues examined it was well under way by the end of the first half hour.

3. A mild inflammatory reaction is demonstrable around wounds made at the time of death when the wound area was not removed until half an hour or one hour has elapsed.

4. The experimental results indicate that the probable factors that influence the early inflammatory response are (*a*) cell injury resulting in a disturbance of the electrochemical equilibrium between leukocytes and damaged cells, (*b*) the liberation of vasodilator substances such as histamine, (*c*) the vascularity of the part and (*d*) the stimulation of the autonomic nervous system.

LIVE FISHES IMPACTED IN THE PHARYNX OF MAN

AN ADDENDUM

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In writing a historical paper, it seems almost impossible to get all the references. In an earlier paper on live fishes impacted in the pharynx of man, I thought that I had brought together and classified by the organs in which the fishes were held, all the known cases (at that time twenty) of this remarkable accident. I had obtained these, in part, as a result of reading Gould and Pyle's "Anomalies and Curiosities of Medicine" (Philadelphia, 1897), and by checking up the whole of the immense "Catalogue of the Surgeon General's Library" for titles of fish for the continuation card catalogue to the "Bibliography of Fishes" by Bashford Dean, C. R. Eastman, A. W. Henn and myself. Furthermore, I had gone through the "Index Medicus" and the "Quarterly Cumulative Index to Current Medical Literature" issued by the American Medical Association, checking, however, only the titles under "Fish" and "Foreign Bodies." Since the article referred to went to press, I have thoroughly checked the forty-five volumes of the "Index Medicus" and the whole set of the "Quarterly Cumulative Index" (to January, 1927) for titles of fish for the "Bibliography of Fishes," and in doing so have brought to light five other specific cases reported in detail in medical journals, six other specific cases with details lacking and a general statement by the outstanding student of oriental fishes. I have recorded these cases in order to make them available for the readers of the preceding article, and to complete the subject.[1]

Since in all the cases to be quoted the fish was found impacted in the pharynx, I have stated this in the title of my article. I shall consider the cases according to the countries in which they occurred.

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1. In this connection it may not be inappropriate to call attention to the utter inadequacy of many titles in medical and zoological literature. I have read literally hundreds of titles, "A Foreign Body in the—Pharynx—Trachea—Esophagus," but only exceptionally did the writer state whether the foreign body was a fish, a button, a safety pin or some other object. Had the foreign body been named, "A Button in the Larynx," every reader would have known that it was a foreign body, and the one interested only in fishes could have passed it by safely. As it is, I fear that among the hundreds of "left-handed" titles that I have looked at (not up), some of them would have been available if the writer had only written thus, "Foreign Body (Fish) in the Throat."

INDIA

In my previous article, it is to be seen that this accident is most frequent in India, Ceylon and Burma, eight cases out of twenty being credited to these three countries. All the cases (save four that are now to be quoted) are from India proper and from farther India (the great Indo-Chinese peninsula). Furthermore, all these accounts apparently relate to the same fish, *Anabas scandens,* the so-called "climbing perch," which is not a perch, and about whose climbing ability there has been much question.

Before taking up these accounts in detail, however, it will be well to quote a nondetailed statement of this kind of accident in India. The scientific name of the fish is not given, but it seems probable that it is *Anabas scandens.* The account is found in a work by W. Pugin Thornton, "Tracheotomy," London, no date, page 60. He states that this accident was narrated as happening at Madras in 1873. The facts given by him are as follows:

> Native fishermen there [in Madras] have a practice of holding in their mouths the fish which they have last caught while they bait their hooks afresh. One of them was doing so when the fish jumped down his throat and stuck there. The bystanders could not withdraw it on account of the prickles on its back, and as no medical man was near to open the windpipe the man was suffocated.

Francis Day (1865), the most profound student who ever wrote on the fishes of India and Indo-China, said of *Anabas scandens:*

> These fishes are common in most pieces of fresh water in Malabar, and esteemed very good eating by the natives, who invariably when catching them bite their heads, in order to destroy life. On one occasion this practice led to a fatal result; the fish having slipped down the throat of the fisherman, it could not be withdrawn owing to the erectile nature of the gill covers and scales, and the man was suffocated before reaching the hospital.

Later (1877) Day makes the following general statement about *Anabas* in his colossal work on Indian fishes:

> Accidents are constantly occurring, due to native fishermen killing these fishes by breaking their vertebral column by a bite, as is done by sportsmen in Europe by striking their heads against their boat. Whilst the fish is in the fisherman's mouth for this humane purpose, (as it is covered by a slimy, slippery secretion), it occasionally slips into his throat, and then owing to its spiny character cannot be withdrawn without extensive laceration of the patient's mouth. Although the following treatment may appear somewhat disgusting it is most successful. Should the fish be still alive, cut off the projecting or caudal part, causing it to die of hemorrhage. When dead the parts easily reached may be removed, but any force employed is most injudicious. An elastic catheter, if necessary, may be passed past the fish, in order to feed the patient, but the decay of the animal is most rapid, whilst a little smell more or less is immaterial to a native of the East.

Of the six specific cases for which I have data one is from Siam, two come from Indo-China and two from Burma. The fish in each of these instances seems to have been *Anabas scandens* and, as noted before, the pharynx was the organ affected. The sixth case is reported from Egypt, but the species of fish cannot be determined.

BURMA

The first Burmese account is related by Shwe Ge, the officiating civil surgeon in 1914 at Pyapon, a town situated on one of the eastern distributaries of the delta of the Irrawaddy. He relates the case as follows:

> A Madrasi coolie boy, aged 14, was brought into the hospital on January 28, 1924 from a village about 3 miles from Pyapon with a history that a live mud fish (climbing Perch?) accidentally got into and was lodged inside the throat. It happened that the boy went out fishing, caught several of these live fish, which he put into a small earthen pot. To prevent these from jumping out of it, he caught hold of one of them, and tried to grind it to death between his teeth. No sooner he opened his mouth, the fish in his hand escaped, dashed forwards and lodged itself inside the throat with his head downwards, there being no chance of its coming out on account of the spikes piercing the throat wall. The patient arrived at the hospital about four hours after the accident, with a very anxious look and in great agony and pain. There was a flow of saliva mixed with blood trickling down from the mouth. On examination into the throat, it was found that the tail of the fish about an inch in length was the only part visible—the head and body being well down in the upper end of the oesophagus.
>
> The throat having been sprayed with local anaesthesia, a pair of tongue forceps was applied to the tail as much as they could possibly catch. Having introduced my forefinger into it, I cut away a few spikes with a pair of curved scissors guided by the finger, but not sufficiently to relieve the fish entirely. A gentle thrust of my finger as well as that of my assistant, on either side, well close upon the spikes, however, entirely relieved the entanglement, so that the traction through the forceps presented no difficulty and the [now] dead fish was removed *in situ*. There was slight laceration for which Pot. Permang. solution was given to gargle, and the patient discharged from the hospital on the 4th February, completely relieved.

The native names of this fish are "Coi" in Bengali and Hindustani, and "Ngabyema" in Burmese, while its common English names are "Mudfish," from its habit of estivating in the mud of ponds during the dry season, and "Climbing Perch" because of its supposed climbing and its actual overland traveling abilities. There can be no doubt that it was *Anabas scandens,* since Day (1877) gives the foregoing native names as in common use for this fish. This particular specimen was 4.5 inches (11.43 cm.) long; 1.75 inches (4.4 cm.) deep and 4.75 inches (12.06 cm.) in circumference.

Shwe Ge's interesting communication concludes as follows:

Although accidents of this kind are extremely rare and unusual, I have been informed that a similar case was brought into a neighboring hospital in 1904, where the patient unfortunately succumbed as the fish could not be successfully extracted.

The next case is recorded by Maung Po Pe, who was subassistant surgeon at a hospital in Zigon, Burma, in 1922, when a Coringhee man was brought to the hospital with acute symptoms of dyspnea, the result of a most extraordinary accident. The account follows:

The man was a fishmonger by trade, and his residence a village near Nattalin. He was returning home with a basket of fish which he bought from a fishery. On his way he stopped to sell some of them. When picking them out of the basket, a live fish leaped up suddenly and found its way into the back of his mouth, partly obstructing the breathing.

A bystander observing the accident tried his best to pull the fish out, but to no avail, the foreign body gliding further down the air passage, and increasing the suffocation.

When he arrived at the hospital about seven hours after the accident, he was in a distressing condition of obstructed breathing. He was unable to speak, he held his head erect and the neck straightened out, and made frequent retching efforts to bring the foreign body out. Glairy fluid and blood tinged saliva flowed from his mouth. Since there was no time to lose, he was seated at once and his mouth opened with a gag to ascertain the exact position of the foreign body.

The greater part of the fish had gone down and only the caudal fin could be felt between the soft palate and the back of the tongue. Traction with a laryngeal forceps failed to bring it out, as the stout pectoral and dorsal fins caught on the soft structures on pulling the fish backwards.

The patient was quickly put on the table, and after a few whiffs of chloroform and painting with iodine, a skin incision, running from the cricoid down to the first two rings of the trachea, was made exactly in the middle line. The cartilages were then divided from below upwards towards the thyroid. There was practically no hemorrhage and division of the isthmus was found not to be necessary.

The distressing symptoms of obstruction were immediately relieved and the patient breathed through the artificial opening. As the foreign body was found too voluminous for the opening intended for its removal, it was extracted through the mouth by passing one finger to dislodge and lift it well upwards, and the other hand setting free the entanglement within the fauces. The skin incision was next closed by sutures.

The patient had a slight aphonia and cough for two or three days, and he was discharged cured on the 16th of March, 1922.

The fish was 3 inches (7.6 cm.) long and 1.5 inches (3.97 cm.) deep at its broadest point, and was of the species called "Ngabye-Maw" by the Burmese. Day (1877) gives this as a vernacular name for *Anabas scandens*. The peculiar feature is the allegation that when the man

leaned over his basket, the fish jumped into his mouth. However, one must not conclude that this was a purposive action on the part of the fish. *Anabas scandens* belongs to a group of fishes called *Labyrinthici*, because they have a labyrinthine water-holding structure in their gill chambers which acts as an accessory breathing organ and enables them to live for a considerable length of time in the air. This species of fish is also extraordinarily active, possibly partly because of this accessory breathing organ, and it just happened that the man's open mouth and the leaping fish coincided and brought about the results stated.

However, this is not the only case of its kind, since in my previous article I recorded that in Burma, in 1878, a fish entered the open mouth of a man swimming in a river. Earlier than this, in 1855, a fish jumped into the throat of a man in Burma while he was swimming.

SIAM

When this article was practically finished I received a letter from Bangkok, from Dr. Hugh M. Smith, formerly U. S. Commissioner of Fisheries and now Fisheries Advisor to the Siamese government. Dr. Smith sent me the following extract from the *Bangkok Times* of Jan. 9, 1924, describing an accident which occurred at Nakon Patna on Jan. 8, 1924. Dr. Smith notes that the fish was *Anabas*.

> Last week a youth of 16 died through being choked by a fish which he had taken out of his net and put head first in his mouth whilst he caught another. The fish which was a *pla mor* of large size, wriggled from the youth's teeth, and slipped down his throat and could not be dislodged though its tail was still presented in the mouth. The gills [the spines on the gill-covers] prevented the withdrawal of the fish and its size prevented its being pushed downwards. The youth died before medical attention could be obtained. It is a common practice to put fish into the mouth in this way.

INDO-CHINA

The first account in Indo-China (1912) comes from the hospital of Cartho, and is written by Lalung-Bonnaire, the operating surgeon in the case. He recounts that on April 1, 1910, it was reported that an Annamite fisherman had swallowed a live fish and was at the point of asphyxiation. However, he thought it an April first joke, until the man was brought to the hospital, and he was called to attend him. The history of the case showed that in order to grasp with both hands a large fish which he was having some difficulty in holding with his foot, the fisherman had put a small fish between his teeth. The fish made some movement which led to a relaxation of the grip of his teeth, and the fish passed down into his pharynx, where it "set" itself by means of its dorsal and pectoral spines.

The surgical aspects of the case are set forth by the author as follows:

> On his arrival the sick man presented the symptoms of an immediate asphyxiation; breathing very accentuated, face red, mouth swollen, eyes wide open and starting from their orbits, blood vessels and muscles of the neck prominent, and thorax bulging. An immediate exploration showed an obstruction in the pharynx caused by the body of a fish, of which one could perceive only the tail portion placed before the tonsils and the posterior pillars of the veil of the palate. Asphyxia became complete while the local doctor, Le Van An, was cleansing the anterior part of the throat. Urgent tracheotomy was affected after painting with tincture of iodine. Once the cannula was in place, I proceeded to the extraction of some fragments by way of the mouth, using the forceps with clamp points. But it was impossible for me before night to get out the whole of the foreign body which, buttressed by the spines of the fins firmly implanted from the back forward, resisted all my efforts. Hence I was forced to postpone till the next day the finishing of the operation. At this time I practiced sub-hyoidean laryngotomy. By this passage, after cutting up the fish with scissors, I succeeded, by using a long curved clamp forceps, in successively extracting the fins, the remainder of the body, and a portion of the head. The snout however, buried in the superior part of the oesophagus, escaped the forceps and was eventually swallowed spontaneously.
>
> The operation ended, I put back the parts of the region in place, but retained the tracheal cannula. In the afternoon lavage of the stomach having brought up débris that had a foul odor, I next administered 180 g. of olive oil to cleanse the digestive tract. The patient's temperature was 38.4°, pulse 94. The night was relatively good in spite of persistent insomnia and the moaning of the sick man. Oedema of the neck was somewhat augmented.
>
> April 3rd, temperature 37.8°, with expulsion through the cannula of abundant purulent mucous secretions. Alimentary canal irrigated.

This treatment was continued for several days. On April 5, the tracheal cannula was removed and the wound dressed, and on the seventh, it was sewed up. On the eighth, the man's voice was almost normal, and he was able to take milk. During the following days, he steadily grew better, and on April 15, he was able to leave the hospital completely cured.

In Annam the fish bears the name "Cà-Ro," but it was identified as belonging to the family *Anabantidae*. It is found in rice fields and ponds as well as in rivers, and is abundant in the markets. Lalung-Bonnaire gives a description of the fish and its habits which leaves no doubts in my mind that it is correctly identified as *Anabas scandens*.

In the following year (1913), Dr. V. Robert, who had read Lalung-Bonnaire's account of his experience, had a similar case in which the fish was clearly identified as *Anabas scandens*. The patient, a native about 25 years of age, had been brought to Tonkin in an ambulance

from Yenbai, a town in about the center of Tonking province. A careful translation of Robert's report follows:

In the morning he had caught some fish with his hands, under a bow net and under a basket in a pool. He had placed between his teeth a fish which he caught intending to deposit it in a receptacle while he continued to fish. The fish in moving slipped between his teeth, penetrated into his mouth and pushed its way deep into the pharynx. In spite of violent efforts at vomiting in the endeavor to expel the animal, it remained solidly fixed in the back part of the throat. About five hours after the accident happened, it was decided to bring in the fisherman by ambulance.

The man was in extreme anguish when he arrived; he was speechless; all movements of deglutition were impossible, and his mouth was wide open. He made vain efforts to expel the foreign body and groaned a great deal. His respiration was very difficult, but nevertheless he showed no signs of asphyxia.

By strongly depressing the base of the tongue one could see the tail of a fish which was lodged securely in the pharynx, firmly fixed there with its dorsum placed against the left lateral wall of the pharynx and its venter against the right lateral wall. It was held immobile in this position by the various fins which, in the course of the repeated efforts at expulsion, had forced themselves into the soft parts.

Extraction by the natural passages was first tried. But all traction on the fish with an instrument risked tearing it to pieces and driving the spines of the fins deeper in. So I decided simply to extract it with my hand. This seemed to be the best method in order to accomplish two things—to disengage the spines, and to assure protection of the mucosa of the pharynx and the mouth in the course of extraction.

Some painting with cocaine was done since the digital exploration of the pharynx provoked some reflex action. The subject was seated on a chair. The index finger, introduced into the mouth, depressed the base of the tongue, located the epiglottis, slipped down along one side of the fish all the way to the head, disengaged the lateral [pectoral?] fin on one side and the ventral fins by pressure from the head backward. The right index finger was then introduced along the posterior surface of the pharynx and disengaged at the same time the dorsal and the lateral fins. In the course of these manoeuvres the sick man made some efforts at vomiting, but respiration, while labored, went on all the time. When the fins were disengaged, I made the patient lean forward and in the course of an effort at expulsion, the fish was ejected, slipping between my two fingers which were holding it, pulling at it, and isolating it from the soft parts.

It was a fish called by the Annamites "Ca gio," measuring 8 cm. in length and provided with a long dorsal fin with needle-like spines [and] with two lateral fins. . . .

The fish removed, the pharynx was again examined in order to make sure that no spines remained sticking in the tissues. The results of the examinations were negative.

The sick man, his pain having ceased and his respiration no longer being impeded, was able to go to a native hospital, to which he was admitted.

He departed thence on September 16, having shown difficulty in swallowing only on the first two days.

EGYPT

The next case is from Egypt. Apparently the fish was not a spiny one, since it was extracted fairly easily. The name "Nile trout" is, of course, a misnomer, no members of the family *Salmonidae* being found in the Nile. Had the writer (Moh. Zaky Shafei) given the vernacular name, it would have been easy to identify the fish in Boulenger's "Fishes of the Nile." Moh. Zaky Shafei gives the following account:

At noon of Aug. 23, 1918, a group of people came to my clinic, carrying a boy . . . 8 years of age, from Talkha, a town on the opposite side of the Damietta branch of the Nile. The boy was nearly dead, and they related to me that he was on the Nile, shore fishing. He caught, first, a small trout, which he carried between his teeth, while he had another in his hand. The first glided in his pharynx and lodged there, and he was asphyxiated. All this took place half an hour before. A colleague, who saw him before I did, suggested opening the pharynx or larynx. I examined him hurriedly, and found the following: Bloody froth about the mouth, face blue, conjunctiva injected, jaws very stiff and extremely difficult to open, muscles of extremities stiff, pulse imperceptible, respirations stridulous, slow, and interrupted, corneal reflex absent, and the boy wholly unconscious.

Treatment.—I first opened the mouth with a gag with difficulty, and introduced my fingers into the mouth. I touched the tail of the fish with the end of my finger, and tried to dislodge it, without success. I then introduced a tongue forceps and pulled with it the tongue, which was thrown backwards. I gave the boy an injection of camphorated oil. I introduced a long broad forceps, caught the tail and jerked it a little and pulled; unluckily the tail had been cut; I tried once more, and got, at last the fish, but, unfortunately the child lost respiration after the fish had been got out. I at once started artificial respiration for twenty minutes, and, happily, animation was restored. I think the loss was due to sudden spasm of the glottis. He remained unconscious for forty-five minutes. I restored his consciousness by all the known means, gave him an injection of strychnine, and warmed him with hot bottles, etc. I examined his throat afterward, and I saw, in different positions in the walls of the pharynx, small abrasions right down to the epiglottis. Then I examined the fish, and I found it to be of the kind called Nile trout; its length was 6 inches, and its greatest breadth [depth] about 3 inches.

I examined the boy on the fourth day, and found him to be in excellent health, and I ordered a gargle of 1 per cent phenol (carbolic acid) and a milk diet for a few days.

HAWAII

On Feb. 3, 1927, daily papers all over the United States contained an Associated Press dispatch from Wailuku, Maui, Hawaii, that a fisherman there had lost his life in similar fashion. Having caught a 4 inch fish (10.16 cm.), he put it in his mouth, while he removed the hook. Before he could put it in his basket the fish pricked him, he relaxed his jaws and the fish passed into his throat and choked him to death.

RAROTONGA, COOK ISLANDS

William Wyatt Gill, the South Sea missionary, gave the following account of the phenomenon in Oceania:

> The only word in the Rarotongan dialect for the nape of the neck is "the killing-place of fish" (*katianga-ika*), in allusion to the immemorial and universal practice of the South Sea Islanders to kill fish caught by the hand by a bite on the neck. Of course, the fish is held laterally for the purpose. Occasionally accidents occur from holding the fish in a wrong way. A short time ago a lad, having secured a small fish, unwisely held the head toward himself. As soon as he opened his mouth to kill it, the fish seeing an apparent mode of escape, darted into his mouth and wedged itself so firmly in the throat that it was impossible (on account of the sharp spines of its dorsal and ventral fins) to get it out. The poor fellow died in great agony on the third day. A young woman on a neighboring island met with her death in a similar way.

SICILY

In my former paper, I noted as the earliest known account of this phenomenon, one published in 1567. Now, however, I can quote a still earlier story. It is found in the "Fisherman," an idyllic poem by the Greek poet, Theocritus, who lived at Syracuse in Sicily in the third century, B. C. He writes of a certain fisherman that:

> Parmis had lured
> A Julis from its rocky haunts, secured
> Between his teeth the slippery pert, when, lo!
> It jerked into the gullet of its foe,
> Who fell beside his lines and hooks and rod,
> And the choked fisher sought his last abode.

SUMMARY

In addition to the twenty cases previously collected and reported, I have added eleven new accounts; of these, two came from each of the following countries, India, Burma and Indo-China, and one from each of the following, Siam, Egypt, Sicily, South Seas and Hawaii. In all cases, the fish was impacted in the "throat" or pharynx; in six, the man or boy died, and in five, he recovered. In three cases of recovery the fish was successfully removed through the mouth mainly by the use of the hand, while in two it was necessary to operate. To the countries noted before in which this practice is not uncommon, must be added Sicily, Egypt, Hawaii, Cook Islands and Siam.

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PRIMARY CARCINOMA OF THE LUNG

REPORT OF A CASE WITH UNUSUAL METASTASES *

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CINCINNATI

Though primary tumors of the lung have been regarded as comparatively rare, interest in these new growths has recently been renewed because of an apparent increase in their incidence. For this reason, and because of the rather unusual distribution of metastases, the case here described deserves to be reported.

There was no suspicion of malignant disease of the lung ante mortem, for the clinical picture was predominantly that of acute nephritis superimposed on an old renal lesion, with secondary cardiac manifestations.

AUTOPSY REPORT

The patient died suddenly eight days after admission to the hospital, and the postmortem examination was made a few hours after death. The body was that of an obese white woman, aged 53. The right lung weighed 575 Gm.; the left, 325 Gm. Examination of the former revealed some puckering of the pleura and induration of the underlying lung tissue, posteriorly, near the apex of the upper lobe. Section through this portion of the lung presented tiny cauliflower-like areas not over from 5 to 8 mm. in the widest extent, which when compressed exuded small drops of grayish, puriform fluid. Elsewhere the lungs were crepitant, with pinkish-gray cut surfaces. The peribronchial lymph nodes were enlarged and anthracotic, with grayish-white, dry, caseous cut surfaces.

The pericardial sac was greatly distended, extending to the left lateral wall of the chest. The measurements were 28 cm. in greatest length, and 20 cm. in greatest width. The sac was filled with approximately 1 liter of serosanguineous fluid. The lining was smooth and glistening, except at one or two points near the base of the heart, where some slight thickening and glazing of the membrane were noted. The heart was small, with a thickened, granular epicardium. A few small varices were seen over the anterior surface of the left ventricle. The chambers and valves were not abnormal. The coronary arteries possessed smooth, glistening linings. The sectioned surfaces of the myocardium were extremely pallid, soft and friable, marked with irregularly distributed fibrous patches and streaks.

Microscopic sections of the lung through the area described revealed a tumor of cylindrical and cuboidal cells, growing in alveolar arrangement with occasional papillary projections and a heavy fibrous stroma. In places the tumor cells were scanty, with extensive chronic inflammatory reaction about them; these areas closely resembled fibroid tubercles. The surrounding air vesicles and bronchi contained small clumps of flattened tumor cells and cellu-

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lar debris. Sections of the peribronchial lymph nodes showed wide-spread tumor masses with papillary projections lined chiefly by cylindrical cells.

Sections of the heart showed a conspicuous increase in connective tissue in the epicardium with lymphocytic and slight endothelial infiltration, which was dense near the periphery. The muscle beneath the epicardium was invaded by tumor cells arranged in large and small alveoli, in some places with papil-

Fig. 1.—Primary carcinoma of the lung; low power magnification.

lary projections, in others with small masses of cells and smaller acini within the alveoli. The tumor cells were large, oval and cuboidal, and possessed large vesicular, round, hyperchromatic nuclei. At one or two points there was a tendency to low columnar arrangement of the cells lining a few of the smaller spaces. Within the deeper layers of the muscle, there were small masses of tumor cells lying within the lymphatic spaces. There were no metastases in other parts of the body.

With a knowledge of the microscopic lesions here described, this case presents a primary alveolar carcinoma of the lung, which on gross examination at autopsy was described as, and mistaken for, an area of tuberculosis. The tumor metastasized by way of the lymphatics to the peribronchial lymph nodes, and thence to the epicardium, which accounted for the roughened, granular surfaces. The small varices were presumably the sites of vascular invasion, and in all probability the rupture of one of these varices, with consequent hemopericardium, resulted in the sudden death of the patient.

CILIATED EPITHELIAL CYST (ECTO-ENDODERMAL) OF THE FLOOR OF THE MOUTH*

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Cysts lined by ciliated epithelium have occasionally been observed in the upper jaw; in such cases either the cyst was in direct communication with the epithelium of the maxillary sinus, or aberrant embryonic sinus epithelium was considered as the origin of the ciliated epithelium. Cysts with such an epithelial lining may also be found in the floor of the mouth and in the tongue; they are etiologically connected with the thyroglossal duct, which is lined by ciliated epithelium. Portions of this embryonic structure, the lower part of which gives rise to the development of the median lobe of the thyroid gland, not infrequently persist patent and sometimes even remain so. Lateral branchings of such persisting portions lined by ciliated epithelium were described by Bochdalek [1] and are known as Bochdalek's tubes. Such tubes may extend to the tip of the tongue and give rise to ciliated cysts in this region, as mentioned by von Recklinghausen [2] and by Neumann,[3] where, also, retention cysts of Blandin-Nuhn's glands occur. The fact that part of the thyroid gland develops from the lower part of the thyroglossal duct also explains the observation that some ciliated epithelial cysts derived from remains of this duct contain thyroid tissue. Misplaced thyroid tissue in the tongue is also the origin of thyroid tumors of this organ.

Branchiogenic cysts, i. e., cysts derived from the branchial clefts, are likewise lined by ciliated epithelium. They occur in the neck, but may push upward and appear in the floor of the mouth.

Cysts originating from remains of the thyroglossal duct may contain squamous epithelium besides the ciliated epithelial cells; this is easily explained by the fact that the outlet of the duct on the tongue, the foramen cecum, is lined by the stratified squamous epithelium of the tongue, which is sometimes continued for some length into the duct.

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* From the Department of Oral Surgery, University of Illinois.
* Read before the Chicago Medical Society, March 2, 1927.

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2. Von Recklinghausen, F.: Untersuchungen über Rachitis und Osteomalacie, Jena, C. Fischer, 1910, Ueber die Ranula, die Cyste der Bartholinschen Drüse und de Flimmercyste der Leber, Virchows Arch. f. path. Anat. **84**:425, 1881.

3. Neumann, E.: Ueber die Entstehung der Ranula aus den Bochdalekschen Drüsenschläuchen der Zungenwurzel, Arch. f. klin. Chir. **33**:590, 1886; Der gegenwärtige Stand der Ranulafrage, Berl. klin. Wchnschr. **79**:26, 1917.

Distinct from these ciliated epithelial cysts are cysts that present not only ciliated cylindric, cuboidal and squamous cells, but also gastric mucosal epithelium and glandular structures resembling mucous, cardiac, gastric and even Lieberkühn's glands. As far as I can ascertain from the literature, the occurrence of such cysts in the oral cavity has never been recorded, and I may therefore assume that the cyst which I am about to report represents an unusual type of oral cyst. It is unusual chiefly with regard to its location, for cysts presenting the features referred to have been observed in the esophagus. Ciliated epithelial cysts of the esophagus form a definite group distinct from other cysts that occur in this part of the digestive tract; they have been carefully studied and described by several writers—Mohr,[4] Zahn [5] and von Wyss [6] —but most extensively by Nakamura.[7] Ciliated esophageal cysts are comparatively large, ranging in size from that of a cherry to that of a medium sized apple. Monolocular and bilocular cysts have been described. In the majority of cases they were congenital. Nakamura describes five different types of epithelium in these cysts, namely, cylindric, ciliated cylindric, cuboidal, squamous and light embryonic squamous epithelium. These various types occur normally in the esophagus at various stages of the embryonic development. Schridde [8] has shown that the first covering of the esophagus consists of a single layer of endodermal epithelium of low cylindric or cuboidal form which is replaced by two layers of cylindric epithelium of high light cells, and these again by ciliated cylindric cells. Then smaller and larger groups of light epithelium in from three to four layers appear, crowd in between the other cells and push forward to the surface. This epithelium is transitory; its desquamation begins in the fourteenth and fifteenth week and is completed at the time of birth. Ciliated epithelial cells can be demonstrated during the entire embryonic life, but desquamation takes place early, and at the same time fibrillar cells appear. Beginning with the thirty-sixth week, intercellular bridges and spaces can be observed. At birth the squamous epithelium is present in from nine to ten layers; in the adult it has twenty-four layers. The endodermal cells of the esophagus are therefore capable of differentiating in five directions and of producing as many types of cells with sharply differentiated morpho-

4. Mohr, R.: Zur Kenntnis der Cysten des Mundbodens und des Oesophagus, Beitr. z. path. Anat. u. z. allg. Pathol. **45**:333, 1909.

5. Zahn, F.: Ueber mit Flimmerepithelien ausgekleidete Cysten des Oesophagus, der Pleura und der Leber, Virchows Arch. f. path. Anat. **143**:171, 1896.

6. Van Wyss, H.: Zur Kenntnis der heterologen Flimmercysten, Virchows Arch. f. path. Anat. **51**:144, 1870.

7. Nakamura, N.: Ueber die Cysten des Oesophagus und ihre Bedeutung, Ztschr. f. ang. Anat. **1**:461, 1914.

8. Schridde, H.: Die Entwicklungsgeschichte des menschlichen Speiseröhrepithels und ihre Bedeutung für die Metaplasie, Münich, J. Bergmann, 1907.

logic characters, namely, high cylindric cells, ciliated cells, polyhedral light cells, cells with protoplasmic fibrils or processes and cylindric mucous cells. As to the occurrence in esophageal cysts of glandular structures resembling cardiac glands, an explanation is found in Schaffer's [9] statement that in 70 per cent of people glands like the cardiac glands are found in the upper part of the esophagus. Also, islands of gastric mucosa with glands like those in the fundus occur in the esophagus. At the cardia, sometimes, typical intestinal epithelium is found, i. e., cells with a striped cuticle, mixed with goblet cells, and these cells are not only on the surface, but also in the glands. The latter are identical with Lieberkühn's glands.

These ciliated epithelial cells with inclusions of glandular structures are mostly congenital and due to misplacement of embryonic epithelial tissue of the esophagus. A few such cysts, however, have been recorded as occurring in old people. For an explanation of their occurrence an observation by Schaffer is of importance, namely, that ciliated epithelium may persist some time after birth in protected parts of the esophagus, for example, about diverticula and excretory ducts of glands.

REPORT OF CASE

A colored boy, aged about 2 years, was referred to me by Dr. R. A. Kordenat of the department of surgery, with a swelling under the tongue forcing it to the roof of the mouth, so that the patient had difficulty in breathing even with his mouth open. He was dull, listless and apathetic; he permitted handling without objection and was not interested in what was going on. The swelling had been aspirated a number of times in the department of minor surgery to give temporary relief. It was congenital and bilateral, and in color resembled a ranula. It occupied the center of the mouth, and extended from the lingual surface of the symphysis of the mandible to the thyroid cartilage.

Under general anesthesia, I removed this growth through the mouth. An incision extending from the chin to the thyroid cartilage would have been more desirable, in that such an approach affords more room and excludes contamination from the mouth, but I believed I could deliver this through his mouth and decided to do so.

A horseshoe-shaped incision along the under surface of the tongue at its junction with the floor of the mouth permitted the peeling of the soft tissues from the cyst membrane. I found that the cyst extended back to the thyroid cartilage. Its capsule was somewhat nodular, the nodules corresponding to a number of cavities found within (fig. 1). Even more interesting was a little wormlike appendix, springing from about the center of the lower surface, running backward independent of the cyst and terminating in a blind end at the thyroid cartilage.

The entire mass, about the size of an average hen's egg, was above the mylohyoid muscle. From the above observations and from the description of the aspirated fluid, I believed this to be a dermoid cyst.

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9. Schaffer, J.: Die Oberen kardialen Oesophagusdrüsen und ihre Entstehung, Virchows Arch. f. path. Anat. **177**:181, 1904; Epithel und Drüsen der Speiseröhre, Wien. klin. Wchnschr. **11**:533, 1898.

The patient made an uneventful recovery. His dyspnea disappeared; he breathed with the mouth closed, and when it was open the tongue was seen occupying its normal place.

Also, a marked mental change for the better was apparent after the operation. His former dulness and apathy were replaced by alertness, playfulness and attempts to talk. He said "baby" and "bye-bye" before leaving the hospital, and learned to feed himself without spilling food. These changes are still progressing.

Fig. 1.—Reduced size wormlike process at side of cyst.

Fig. 2.—Interior of the cyst showing the variously sized loculi; natural size.

Cysts of this type, as may be inferred from the report, are not described in the textbooks, nor, as mentioned, does the literature show a report of such a case occurring in this location. The growth originated during the development of the embryo, probably through the formation and separation of a bud at the point of fusion of the stomodeum and enterodeum. The cells composing this bud proliferated, and the tumor mass developed, which, on section, presented a number of cystic cavities

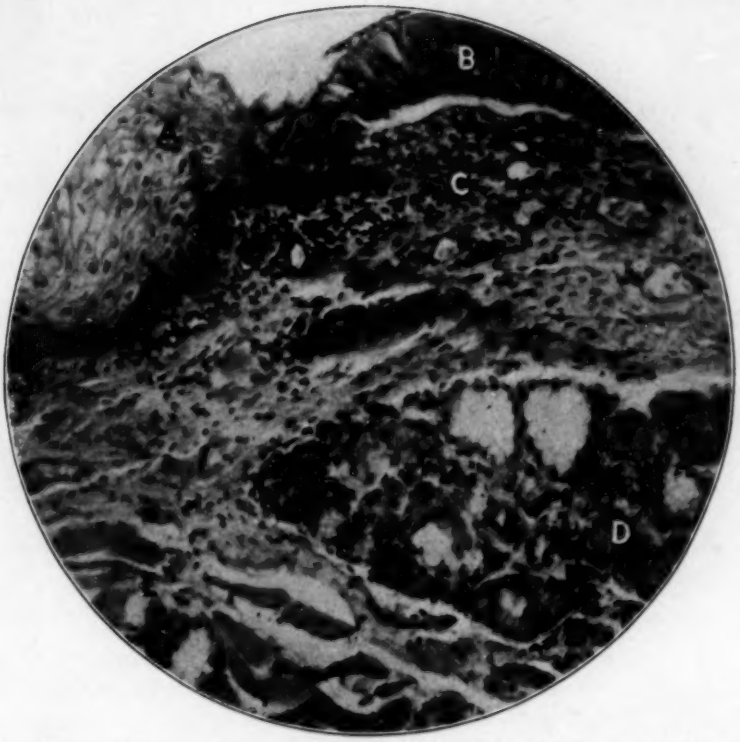

Fig. 3.—*A*, indicates squamous epithelium; *B*, high columnar epithelium, with a cuticular border, containing cells filled with a yellowish brown pigment; *C*, lymphoid tissue; *D*, salivary gland tissue; *E*, muscularis. Magnification, 150.

Fig. 4.—*A* indicates high columnar epithelium like that of the gastric mucosa; *B*, glandular tissue resembling Brunner's glands. Magnification, 150.

—a multilocular cyst (fig. 2) in which cells were found derived from the stomodeum, similar to the salivary gland cells, and from the enterodeum, identical with Brunner's gland cells (fig. 3).

SUMMARY

This report concerns a congenital cyst of enterogenic and ecterogenic origin, lined by squamous, columnar and ciliated epithelium, and containing glandular structures of the salivary and intestinal glandular types (fig. 4). An interesting feature was the presence of a yellowish brown pigment in the ciliated epithelial lining. The walls proper consisted of a lamina propria and muscularis which in one region formed a thick layer at a point where several compartments met. This corresponds to a feature that is always found in the esophageal cysts that have been described.

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PATHOLOGIC ANATOMY OF SYPHILIS OF THE PULMONARY ARTERY

REPORT OF A CASE AND REVIEW OF THE LITERATURE *

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The present knowledge of syphilis of the large vessels is largely due to the work of Heller,[1] Benda [2] and Chiari.[3] In its clinical and pathologic-anatomic significance, it is mainly a question of aortic syphilis.

Syphilitic disease of the aorta has two well characterized forms: a gummatous aortitis and a productive, scar-forming type. The former shows macroscopic gummas as its characteristic form, while the latter, on microscopic examination, is seen as syphilitic granulation tissue with eventual induration and contracted scar formation.

The macroscopic picture of aortic syphilis is well known and need not be considered here. One needs only to mention that, in contradistinction to atherosclerosis, the processes are often found in greater numbers in the segment from above the valves to the arch. The seat of the syphilitic disease is preponderantly in the media and adventitia. The infiltration is usually found around the vasa vasorum, and seldom involves the intima.

The intima itself takes only a small part in the inflammatory process. It is diffusely thickened by the symmetrical laying down of collagenous connective tissue fibers containing but little of elastic tissue elements. The overlying intima may be drawn down into funnel-shaped scars, show fine wrinkling or be elevated and depressed in wavelike areas in accordance with the severity and type of the disease of the media.

Spirochetes in the wall of the vessels affected by syphilis can be demonstrated by the Levaditi method. They lie in newly formed granulation tissue which as yet shows no regressive changes, and they are seen between the fibrils or in the lymph spaces. They can also be demonstrated near the necrotic tissue in the wall of the vessel.

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* From Pathologic Institute of the Friedrichshain-Hospital, Berlin; Prof. Dr. L. Pick, Director.

1. Heller, A.: Die Aortensyphilis als Ursache von Aneurysmen, Verhandl. d. deutsch. path. Gesellsch. II., München 1899; München. med. Wchnschr. **50**:1669, 1899; Aortenaneurysma und Syphilis, Virchows Arch. f. path. Anat. **171**:177, 1903.

2. Benda, C.: Aneurysma und Syphilis, Verhandl. d. deutsch. path. Gesellsch. **6**:164, 1903.

3. Chiari, H.: Ueber die syphilitischen Aortenerkrankungen, Verhandl. d. deutsch. path. Gesellsch. **6**:137, 1903.

TABLE 1.—*Group 1: Proved Cases of Syphilis of the Pulmonary Artery*

Case	Author and Year	Age and Sex	Clinical Diagnosis	Condition of Heart on Section	Macroscopic Appearances of Pulmonary Artery	Microscopic Appearances of Pulmonary Artery	Condition of Aorta	Syphilis in Other Organs
1	O. Weber, 1863..... (Allg. med. Centralzeitung **32**: 822, 1863)	.. ♀	Secondary syphilis treated	Not given	Stenosis of inferior branch right pulmonary artery; bean-sized gumma projecting in lumen; intima otherwise free; media thickened far into lung	Thickening due to hyperplastic media elements; nodule in media; intima over it thin but intact	Not given	Syphilitic changes in skull; gummas in the liver
2	Wagner,[11] 1866	31 ♂	Constitutional syphilis 18 years	Syphiloma on septum and aortic surface of left auricle	One pea-sized, more smaller gummatous nodules between two of the pulmonary valves; pouch 1½ inches wide containing small gumma on pulmonary trunk; small gummatous nodules in first part of left pulmonary branch; lumen somewhat narrowed	Not given	Moderate atheromatosis	Gummas on tongue and pectoralis major; radiating scars in liver; scars on bone
3	Schwalbe, 1890 ..... (Virchows Arch. f. path. Anat. **119**: 271, 1890)	53 ♀	Aortic insufficiency and stenosis; pericarditis	Gummatous myocarditis and endocarditis of pulmonary conus; stenosis of pulmonary valves	Pulmonary artery stenosed; radiating scars from mouth of pulmonary artery to right branch; seven millet-seed-sized gummas extending from side to side, shining through	Adventitia: increased nuclear proliferation; media: muscle fibers covered by round cells; lentil-sized nodule broke through intima, forming hump; intima damaged; nodule surrounded by round and spindle cells	Aneurysmal dilatation of first part of aorta; severe arteriosclerosis of aortic system	Scars on forehead
4	Kasem-Beck, 1900 ..... (Centralbl. f. inn. Med. **21**: 593, 1900)	50 ♂	Grave cardiac decompensation	Heart free	Lumen narrowed; intima uneven; pea-sized gumma in wall; section of wall shows scar tissue and granular nodules	Wall thickened; gumma formation; no other description given	Closely adherent to pulmonary artery; widened and atheromatous	
5	Wagner and Quiatkowski,[12] 1903	49 ♂	Syphilis four years untreated; malaria: polyarthritis	Gummas; chronic myocarditis	Twelve cm. in diameter; wall irregularly thickened up to 7 cm.; intima thickened and uneven, showing scattered flat plaques which on cross section showed yellowish cheesy layers	Intima thickened; necrotic parts surrounded by infiltrations of granulation tissue; giant cells; granulation tissue in upper layers of media; granulation tissue of adventitia; endarteritis of vessels up to obliteration	Aortitis; cellular infiltration of intima; endarteritis of vessels of adventitia	Syphilitic scars in liver
6	Handford, 1904 ..... (Brit. M. J. **31**:	32 ♀	Cardiac decompensation; arrhyth-	Extensive gummas	Over pulmonary valves projecting into lumen	Nodule consisted of necrotic cheessy mass in	Dilated atheromatous	

	1745, 1904)		mia; heart block convulsions		was a small nodule in intima	intima surrounded by granulation tissue, which in turn was surrounded by a fibrous layer; endarteritis and periarteritis		
7	Stockmann (Benda) 1904 (Ueber Gummiknoten in Herzfleische bei Erwachsenen, Wiesbaden, 1904)	35 ♀	Septopyemia	Gummas	Bean-sized gumma at base of valves in sinus Valsalva	Gumma in intima consisted of necrotic tissue surrounded by connective tissue; intima destroyed, in upper parts remnant of elastic fibers	Wall enormously thickened; mesa-ortitis	Smooth atrophy at base of tongue
8	Hart, 1904 ..... (Virchows Arch. f. path. Anat. **177**: 205, 1904)	32 ♂	Treated for years for florid syphilis	Free	2.5 by 1 cm. gummatous nodule projected into lumen; wall closely grown to aorta; in other parts wall is thinned	Round cell infiltrations around vasa vasorum; media thickened through granulation tissue, containing leukocytes and giant cells; nodule contained necrotic cheesy material, included intima and destroyed it; elastica interna also destroyed there	Aneurysm of ascending aorta	Gummatous tracheitis and bronchitis with stenosis; scars in larynx; gummas of sternum and vault of skull; syphilitic periostitis of tibia bilateral; scars in liver
9	Henschen,[8] 1906	42 ♀	No symptoms of syphilis; influenza; rheumatic arthritis; pleuritis	Free	Dilatation of pulmonary trunk with great thickening of wall; radiating deep scar on intima	Thickening due to richly cellular granulation tissue	Sclerosis	Indurated masses in mediastinum extending to posterior wall of pulmonary artery
10	Barth,[7] 1910	57 ♂	Progressive cerebral paralysis; pleuritis	Free	Aneurysm 6 cm. long and 3.5 cm. wide; depressions and fine wrinkling of intima; right branch widened; left narrowed; indurated connective tissue between aorta and pulmonary artery	Sclerosis of whole wall with thinning in area of aneurysm; media destroyed; scattered areas of round cell infiltrations in adventitia; scarlike areas in media surrounded by elastic fibers; elastica interna sclerotic	Intimal thickening	
11	Warthin,[9] 1917	37 ♂	Syphilis of lung	Bovine heart, 700 Gm.; myocarditis	Pulmonary artery much dilated and markedly sclerotic; division to left upper lobe showed aneurysmal dilatation	Pulmonary artery and its division showed syphilitic arteritis identical with syphilitic mesa-ortitis; Spirochaeta pallida in wall of sac toward adventitia	Typical syphilitic mesa-ortitis	Hepatitis with multiple gummas; adrenalitis and orchitis
12	Peck, 1927	60 ♀	Grave cardiac decompensation	Fragmentation of heart muscle with scarlike areas	Irregular diffuse thickening of wall; intima showed cushion-like elevations with whole lumen narrowed; thrombosis of right branch; widening of left branch; crevice-like defect of intima over anterior sinus Valsalva	Necrotic gummatous masses in intima; media thickened through granulation tissue; adventitia thickened; vasa vasorum showed periarteritis and endarteritis	Light sclerosis	Base of tongue smooth

Aortic syphilis is a rather frequent condition. Oberndorfer [4] found it in 7 per cent of all cases coming to autopsy. Stadler [5] found 82 per cent in over 200 cases of syphilis, while Chiari [3] reports 59 per cent from his syphilitic material.

In comparison with the relative frequency of aortic syphilis, the localization of syphilis in the pulmonary artery is a rarity.

An etiologic relationship between the syphilitic inflammations of the pulmonary artery and the infrequent aneurysms of that vessel is supported by the work of Posselt.[6] However, here, even much more than in the aorta, simple arteriosclerosis plays a basic and essential rôle. Only three cases of pulmonary syphilis (Barth,[7] Henschen [8] and Warthin [9]) which macroscopically and microscopically give pictures comparable to aortic syphilis have been reported in the literature.

With the exception of these three cases, the condition that has until now been reported as recognizable syphilis of the pulmonary artery has usually presented itself in the form of arteritis pulmonalis gummosa. Cases of syphilis of the pulmonary artery have been described, however, in which the authors themselves admit the absence of syphilitic histologic stigmas and in which they fail to state the differences from the ordinary arteriosclerosis. They based the diagnoses mainly on what they considered accompanying syphilitic pathologic-anatomic observations in other organs or by syphilis in the history.

Only twenty-nine cases, including the one reported here, were found in a review of the international literature on syphilis of the pulmonary artery. They have been divided into three groups. In group 1 (table 1) were included those cases in which the diagnosis of syphilis of the pulmonary artery was considered justifiable from the macroscopic or microscopic description given by the authors. The two cases in group 2 (table 2) were considered secondary extensions of the syphilitic or gummatous processes from adjacent areas, such as mediastinal structures, but the criteria for the diagnosis of syphilis were present. In the last group (table 3) were placed those cases in which the diagnosis was

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4. Oberndorfer, M.: Luetische Aortenerkrankung und Aorteninsuffizienz, Berl. klin. Wchnschr. **49**:2501, 1912.

5. Stadler, E.: Die Klinik der Syphilis, Arb. a. d. med. klin., Jena, G. Fischer, no. 1, 1912.

6. Posselt, A.: Die Erkrankungen der Lungenschlagader, Ergebn. d. allg. Pathol. u. path. Anat. **13**:298, 1909.

7. Barth, H.: Ein Fall von Mesarteriitis luetica der Arteria pulmonalis mit Aneurysmenbildung, Ztschr. f. Path. **5**:139, 1910.

8. Henschen, S. E.: Das Aneurysma arteriae pulmonalis, Volkmann, Klin. Vorträge, 422-423, Innere Med., no. 126-127, p. 597, 1906.

9. Warthin, A. S.: Studies of the Pulmonary Artery: Syphilitic aneurysm of Left Upper Division: Demonstration of Spirochete Pallida in Wall of Artery and Aneurysmal Sac, Am. J. Syph. **1**:693, 1917.

TABLE 2.—*Group 2: Syphilis of Pulmonary Artery by Extension*

Case	Author and Year	Age and Sex	Clinical Diagnosis	Condition of Heart	Condition of Structures Around Pulmonary Artery	Condition of Pulmonary Artery	Condition of Aorta	Syphilis in Other Organs	Remarks
1	Friedreich, 1859 (In Lang: Die Syphilis des Herzens, Wien, 1889)	30 ♂	Cardiac decompensation; sudden death	Fibrogummatous myocarditis; nodule in right auricle; fibrogummatous pericarditis	Connective tissue of mediastinum showed callous induration and scattered gummatous nodules	Callous connective tissue surrounded pulmonary trunk; narrowing of lumen over valves	Root closely surrounded by indurated connective tissue studied with gummas; ascending aorta dilated and atheromatous	.....	.....
2	Fittje, 1904..... (Verblutung aus der durch zerfallendes Gumma eröffneten Pulmonalarterie, Kiel, 1904)	34 ♂	Contusion of chest and abdomen; ten weeks later sudden death	Free.....	Fibrous connective tissue masses in tissues of interior wall of chest extending into muscles of breast; cheesy nodule 7 by 4 by 1 cm. on inner side of sternum	Caseous bronchial nodes rupturing into bronchus and into pulmonary artery through 7 mm. cleft	Ascending aorta thin; descending aorta buckled with focus-like, depressed grooves	Scars on anterior part of breast; scars on surface of liver; left testicle caseous; right inguinal nodes	Bleeding to death from opening of pulmonary artery by necrotic gumma

TABLE 3.—*Group 3: Doubtful Cases of Syphilis of Pulmonary Artery*

Case	Author and Year	Age and Sex	Clinical Diagnosis	Condition of Heart on Section	Condition of Pulmonary Artery Macroscopically	Condition of Pulmonary Arteries Microscopically	Condition of Aorta	Syphilis in Other Organs	Remarks
1	Virchow, 1858... (Virchows Arch. f. path. Anat. **15**: 217, 1858)	22 ♀	Syphilis 3½ years before examination; typhus	Free.....	Hard bluish nodule over line of closure of pulmonary valves	Not given	Not given.....	Rash suggestive of syphilis; scar in cervical canal	Nodules on wall of pulmonary artery may or may not have been syphilitic
2	Dickinson, 1862 (Tr. Path. Soc. London **13**: 60, 1862)	40 ♂	Pain in right side of chest; cough; dyspnea; systolic murmur at base of heart	Pericarditis; fibrous thickening of walls of heart; fibrous nodules around oartic valves	Fibrous thickening of intima which was roughened up to its bifurcation; lumen of right branch narrowed to size of coronary artery and filled with fibrin masses in smallest branches	Thickening consisted mostly of irregular masses of uncertain structure, also some kernel-sized bodies; fatty infiltration	Not given.....	A myeloid liver	Doubtful case of syphilis; heart and pulmonary artery diseased
3	Payne, 1874..... (Tr. Path. Soc. London **25**: 49, 1874)	33 ♀	Bronchitis; puerperal infection; pulmonary disease	Not given.....	All branches of pulmonary artery surrounded by fibrous thickenings; (right lower lobe) a belt ¼ inch wide of grayish tissue with greenish yellow center surrounded the main branch	Periarterial masses resembled syphilitic granulation tissue; intima unchanged	Not given.....	.....	Author thinks syphilis not ruled out
4	Gregorjev, 1886 (Med. Obozr. **25**: 3, 1886)	34 ♀	Probably syphilis, but denied	Free.....	Egg-sized aneurysm of pulmonary artery; mouth of vessel blocked by calcium plaques; dilated up to bifurcation	Not given	Not given.....	Not given.....	.....
5	Wallis, 1889..... (Cited by Posselt [6])	13 ♀	Father had had syphilis; she was without stigmas	Free.....	Changes of the lumen; thickening of wall, especially of media and adventitia	.....	Aorta-like pulmonary artery	Not given.....	Original not available; cited by Posselt
6	Sequeira, 1897... (Tr. Path. Soc. London **48**: 58, 1897)	37 ♂	No previous symptoms; sudden death	Free.....	Lumen narrowed by a 3.5 by 5 cm. tumor in wall of artery above valves; covered by intima	Intima intact; large spindle cells with long nuclei; giant cells along the vessels; round cell infiltrations; many vessels thrombosed	Not given.....	Not given.....	Diagnoses between sarcoma and gumma; considered the latter
7	Brünning, 1901 (Beitr. z. path. Anat. u. z. allg. Pathol. **30**: 457, 1901)	54 ♂	History of syphilis; pneumonic croup; fibrous pleurisy	Free.....	Thickened wall; extreme sclerosis patchy	Intima thickened to smallest branches; elastic fibers strongly developed	General arteriosclerosis	Not given.....	.....
8	Brünning, 1901 (Beitr. z. path. Anat. u. z. allg. Pathol. **30**: 457, 1901)	72 ♂	Apoplexy; lobular pneumonia	Free.....	Arteriosclerotic thickening of intima	Main branches of pulmonary artery showed intimal thickening; considerable number of prominent elastic fibers parallel to elastica interna; smallest vessels free	Severe arteriosclerosis	Interstitial orchitis; interstitial hepatitis	.....

						elastica interna; smallest vessels free				
9	Loveland, 1901 (M. Rec. **59**, no. 9, 1901)	51 ♂	Syphilis in history; gonorrhea; oral carcinoma; aneurysm; blood poisoning two years before examination	Free.....	Total dilatation of pulmonary artery; wall thin; calcium deposits; aneurysm of right branch with rupture at hilum	Not given	Atheromatous deposits	Not given.....	.....
10	McPhedran and Mackenzie, 1903 (Cited by Posselt [6])	55 ♂	Death due to rapidly spreading pulmonary disease; infarcts in lung	Not given.....	Plaque-like intimal thickening of trunk and larger branches; endarteritis and thrombosis smaller branches	.....	.....	Miliary gummas in liver	Cited by Posselt
11	Westenhoeffer, 1906 (Deutsche med. Wchnschr. **32**, no. 4, 1906)	34 ♀	.....	.. ..	Syphilitic condition; no other statement given	Not given	Syphilitic condition in whole aorta; hempgrain gumma near superior mesenteric artery; another in middle right common carotid	Syphilis of both subclavians; left obliterated; brain artery free	.....
12	Brooks, 1907.... (Proc. New York Path. Soc. **7**: 177, 1907-1908)	34 ♀	Hemorrhage in brain with hemiplegia; abortion at 8 months	Free.....	Moderate dilatation over pulmonary ostium; yellowish sclerotic plaques in all branches extending into lumen; wall thickened and fibrosed	Wall thickened without interruption, whole trunk and branches; no other statements	Aorta and larger vessels narrower than usual; arteriosclerosis	Arteriosclerosis of vessels of brain	Author attributes changes to syphilis
13	Rogers, 1908..... (Quart. J. Med. **2**, no. 5, 1908-1909)	38 ♂	Syphilis; rheumatism	Free.....	Pulmonary ostium wide; middle pulmonary leaflet almost destroyed; wall thick and leathery; intima rough and opaque, irregularly thickened; hourglass dilatation of wall	Not given	Free.....	Free.....	Author thinks no doubt of syphilis in this case
14	Ploeger, 1910.... (Frankfurt. Ztschr. f. Path. **4**: 286, 1910)	52 ♀	Heart disease 22 years following delivery; old periostitis in left leg	Free.....	Tough thrombus on wall 3 cm. above pulmonary valves; dilatation above and below thrombus; intima above thrombus shows plaque-like deposits, also seen in smallest branches	Round cell infiltrations, especially in adventitia; obliteration of vasa vasorum; adventitia and media breaking down; irregular thickening of elastic fibers	Scarring and degenerations; small saclike aneurysm of aorta ascendens	Small calcified aneurysm of artery lienalis	Fits description of arteriosclerosis
15	Lombardo, 1914 (Zentralbl. f. d. ges. inn. Med. u. d. Grenzgeb. **10**: 115, 1914)	45 ♀	Cirrhosis of liver; nephritis; uremia	Multiple gummas..	Severely thickened wall; an evident symptom of a chronic inflammatory process	Not given; not examined	Aorta-like pulmonary artery	Cirrhosis of liver with ascites	.....

uncertain, through either unsatisfactory macroscopic or microscopic descriptions, or in which the descriptions would just as well have fitted atheromatous or atherosclerotic changes.

Posselt,[6] in his much quoted work, has reviewed the cases of syphilis of the pulmonary artery until 1909, but without any critical separation according to the points I have brought out. Barth [7] has also covered the literature up to 1910. Jores,[10] in the Henke-Lubarsch system for 1924, reviews the subject and refers to Wagner,[11] Wagner and Quiatkowski [12] and Posselt [6] for his literature. The present report has covered all the available literature until 1927, and the paucity of cases since the last report is striking.

REPORT OF A CASE

History.—A woman, aged 60, was brought to the second medical clinic on July 7, 1924 (Director, Prof. Dr. Pf. Richter) with marked cyanosis, cardiac decompensation, breathlessness and rapid pulse. Shortly after admission she died. Her relatives said that her husband was dissolute. There was no history of abortion. She had two children living and well. At the age of 32, shortly after the birth of one of her children, she had developed ulcers of the leg, which recurred in later years. She had had heart disease for eight years and a frequent cough for three years. She lost consciousness four weeks before her death, and from that time her legs and abdomen had been swollen.

Anatomic Diagnosis.—Diffuse gummas of the trunk of the pulmonary artery with obliterating thrombosis of the right main branch; slight syphilitic sclerosis of the left branch; dilatation of the heart, especially of the right side, with hypertrophy of the right ventricle; slight fibrosis of the mitral and aortic valves; open foramen ovale; sclerotic spots on the coronary arteries and in the thoracic aorta; hydropericardium; bilateral hydrothorax; ascites; cyanotic induration of the spleen; smooth atrophy of the base of the tongue; numerous old pleural adhesions, especially on the right side; tuberculous bronchopneumonia leading to fibrous scars in the right middle and lower lobes; stasis and parenchymatous degeneration of both kidneys; fresh hemorrhages in the mucosa and in the inner muscular layer of the uterus; circumscribed thickening of the fibrous capsule of the left lobe of the liver; old adhesions around the gallbladder.

Necropsy.—(Performed by Prof. Dr. Ludwig Pick, Sept. 7, 1924.) The body was that of a medium-sized woman, and was in good condition. Subcutaneous fat was well developed. Postmortem contraction was not present. Postmortem cyanosis was present, with distinct cyanosis of the ends of the fingers and of the ears. The musculature was well developed. The abdominal viscera were in normal position; the diaphragm was in the right sixth and in the left fifth intercostal space. There was a moderate quantity of fluid in the abdomen, and the appendix was normal. Slight adhesions were found between the gallbladder and the peritoneum.

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10. Jores, L.: Arterien, in Handbuch der speziellen Pathologie Anatomie und Histologie, Berlin, F. Henke und O. Lubarsch, 1924, vol. 2.

11. Wagner, E.: Das Syphilom im Allgemeinen, das Syphilom des Herzens und der Gefässe im Speziellen, Arch. d. Heilkunde. **7**:518, 1866.

12. Wagner, R. E. and Quiatkowski, G. J.: Ueber einen Fall von Syphilis des Herzens mit bedeutender Erweiterung der Arteria pulmonalis, Virchows Arch. f. path. Anat. **171**:369, 1903.

The spleen measured 10 by 6 by 2.5 cm. and was firmer than normal. It was bluish red on section and showed well marked trabeculae; follicles were not seen. The suprarenals were normal.

The left kidney measured 11 by 4 by 3 cm. The capsule stripped easily; it was of flabby consistency and the surface was smooth. On section the cortex was found to be of ordinary width and was light grayish yellow. The pyramids were dark red, and the markings were well preserved.

The right kidney measured 12 by 4 by 2 cm., and presented the same conditions as the left. The ureters, bladder and vagina were normal. There was fresh blood in the muscles around the fundus of the uterus, and mucous membrane over this area. The muscular wall was not thickened. The tubes were patent, and the ovaries were normal. The pouch of Douglas and the rectum were normal.

The stomach, the duodenum, papilla of Vater, the bile ducts and the pancreas were normal. The portal vein and hepatic artery were normal.

The liver measured 25 by 19 by 6 cm. The part of the capsule against the right ribs showed a white, thickened, palm-sized area; the consistency was normal. On section, the lobules appeared well defined, and yellowish brown. From one half to three fourths of a liter of a serous fluid was found in both pleural cavities. The lungs were adherent to the thoracic walls by flat, stringlike adhesions, especially on the right side. Both lungs were a little enlarged and somewhat heavy, containing air without augmented consistency. In the right middle and lower lobes singles nodules, hazelnut-sized and smaller could be felt. On section they were a reddish brown, and on pressure a bloody, air-containing fluid was expressed. In the place in which the indurated areas were felt in the parenchyma of the right lung slategray, firm nodules were seen, in which were embedded numerous grayish-white, pinhead-sized tubercles. The bronchi were normal. The branches of the pulmonary artery and the veins in the parenchyma of the right lung were smooth and normal.

When the lungs were removed, it was seen that the branches of the right pulmonary artery which entered the lung were completely thrombosed. Nothing was to be seen of the lumen.

The pericardium contained about 50 cc. of serous fluid. The epicardium and pericardium were smooth and shining.

The trunk of the pulmonary artery was much thickened, and felt firm. The heart was much enlarged. Dark blood was expressed from the chambers of the heart. The heart was examined together with the aorta. The left ventricle and auricle were dilated. The thickness of the wall of the left ventricle was 1.2 cm. and that of the right ventricle was 0.5 cm. The mitral and aortic valves showed a diffuse thickening of moderate degree. The endocardium was normal. The heart muscle was prevailingly grayish red. The right ventricle was much dilated. The papillary muscles and trabeculae were distinctly flattened. There was a similar dilatation of the right auricle. The tricuspid was normal. The pulmonary valves were not thickened to any extent, and the right medial lunula was fenestrated (fig. 2).

While the heart muscle showed no infiltration, the trunk of the pulmonary artery was seen to be changed in a striking and extreme measure. The changes began immediately over the valves (fig. 1).

The usually relatively thin wall of the pulmonary artery showed a diffuse, callous-like thickening of unequal degree.

The intima was irregularly elevated by a number of flat and sometimes cushion-like masses of a firmly elastic consistency. The whole lumen was narrowed. At the point of bifurcation of the right pulmonary artery there was a

Figure 1

Figure 2

Figure 3

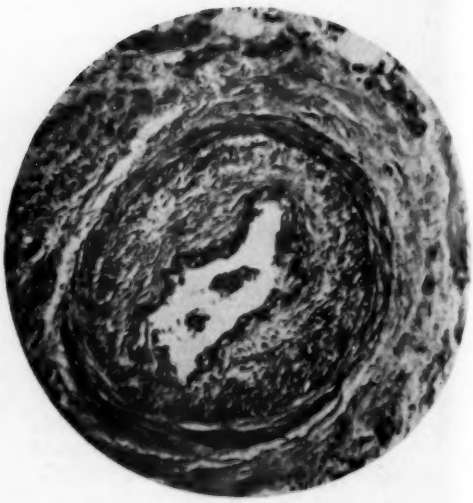

Figure 4

Fig. 1.—Opened right ventricle showing the narrowing of the trunk of the pulmonary artery by multiple gummas.

Fig. 2.—Pulmonary ostium showing narrowing from gummous arteritis.

Fig. 3.—Microscopic section through the wall of the pulmonary artery (left) with a gumma projecting into the lumen. The media is seen as a dark band. The formation of gummas is essentially an intimal process. Ten per cent formalin, paraffin, Weigert's elastic stain-carmine; low power magnification; × 7.

Fig. 4.—Syphilitic endarteritis in the wall of the gummatous pulmonary artery. The technic used was the same as in figure 3. Leitz objective 4, ocular 2.

deep retraction, and the branch itself was completely closed. The corresponding left branch was widened, and its wall did not show the diffuse thickening seen in the main trunk; but for a distance of 1.5 cm. from its point of origin, the intima was still grayish yellow and showed induration and irregular elevation. There was a crevice-like defect of the intima of the main trunk immediately over the anterior sinus of Valsalva. It was lentil-sized, with slightly jagged edges, which entered fairly deeply into the thickened wall (figs. 1 and 2).

A longitudinal section was made through the whole length of the trunk and the left branch in a line corresponding to the middle of the right pulmonary leaflet. The greatest thickening measured 2 cm., and the transparent, indurated masses with their yellowish areas of infiltration were outlined by the yellowish, still intact wall of the pulmonary artery.

The main branch of the right pulmonary vein was filled with solid grayish-red masses of thrombi.

The ascending aorta, the arch and the trunks of the other large vessels were smooth and normal. On only part of the isthmus of the aorta were there grayish, sclerotic intimal thickenings which were partly arranged in a typical form around the exit of the intercostals.

The coronary arteries were widened, and yellowish-white deposits were scattered on the intima.

The base of the tongue was smooth. The soft palate with the uvula, tonsils, the pharyngeal mucosa, œsophagus, larynx, trachea and thyroid were normal.

Microscopic Examination.—The preparations were preserved according to the method of Pick. For purpose of examination a piece was cut through the entire wall of the pulmonary artery along its longitudinal axis corresponding to the area of greatest thickness and including adjacent portions which were not so thick. Sections were also taken from the thrombosed right branch and from its branches supplying the upper and lower lobes, the heart muscle, the left branch and the parenchyma of both lungs. The sections were embedded in paraffin and stained with hemalum-eosin, Van Gieson's stain, resorcin-fuchsin after Weigert, and counterstained with alum carmine, and Levaditi stains.

After staining with Weigert's elastic stain, the media of the original wall of the artery could be seen macroscopically as a well differentiated band. It was noticeable that the main part of the thickening and especially the elevated areas were situated internal to the media (fig. 3). Generally speaking, even at the places in which gumma formation was macroscopically most noticeable the media was preserved fairly well.

The adventitia was thickened, and consisted of a heavy nucleus and poor connective tissue, for the most part concentrically arranged around the longitudinal axis of the vessel. Here and there fat grapelets were enclosed. In the outlying parts especially were found circumscribed areas of round cell infiltrations, many of them perivascular. Somewhat larger arteries and veins were present, usually with a more or less thickened intima, which sometimes caused complete closure. This intimal thickening consisted of a rather loose connective tissue which contained a moderate amount of spindle cells, and which was sharply differentiated from the muscular coat of the media in the smaller arteries. In these vessels the elastic stain revealed the closed ring of elastica interna between the thickened intima and the media. This ring was often split up into several layers, and also formed in rings. Especially well formed was a circular elastic formation situated immediately below the endo-

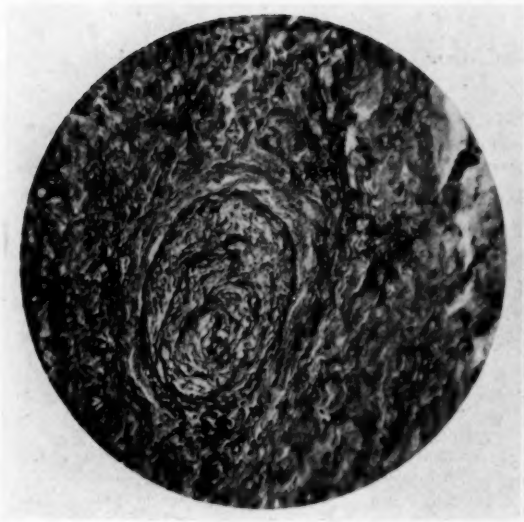

Figure 5

Figure 6

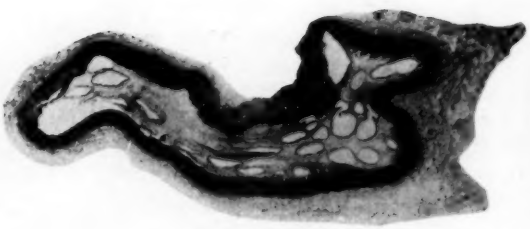

Figure 7

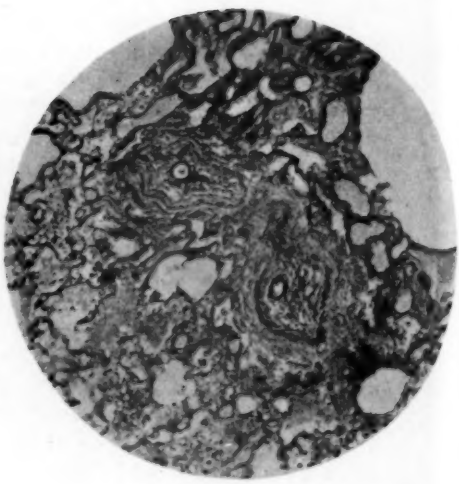

Figure 8

Fig. 5.—Syphilitic endophlebitis in the wall of the gummatous pulmonary artery. The technic was the same as in figure 3. Leitz objective 4, ocular 2.

Fig. 6.—Damage and rupture of the elastic fibers (dark) by syphilitic granulation tissue (light) in the media of the gummatous pulmonary artery. The technic was the same as in figure 3. Leitz objective 3, ocular 2.

Fig. 7.—Cross-section of the branch of the pulmonary artery to the right upper lobe. Endarteritis obliterans syphilitica with recanalization. The technic was the same as in figure 3. Low power magnification; × 10.

Fig. 8.—Section of the parenchyma of the right lower lobe. Endarteritis obliterans syphilitica of the small arteries of the lung. The technic was the same as in figure 3. Leitz objective 3, ocular 2.

thelium of the narrowed lumen. The small veins were completely closed, and there was a new formation of elastic elements from the elastic tissue (figs. 4 and 5).

Many areas in the media were fairly well preserved and free from infiltrations and necrosis; the nuclei and elastic fibers took a fairly good stain. Those areas corresponded to the places in which there was relatively little thickening of the wall of the pulmonary artery. In the area of intimal thickening all types of microscopic changes were found. Granulation tissue, not characteristic, rich in small round cells, grew out in small strips from the adventitia into the media. Besides round cells, they contained fairly numerous plasma cells, which in some parts developed to such a size that they divided the media. Thus in those places the elastic elements of the media were cut up into small irregular fragments embedded in the mass of granulation tissue (fig. 6). In the granulation tissue inside of the original media were found small vessel trunks narrowed by intimal proliferation, sometimes going on to total closure.

Where there was a moderate thickening of the wall of the artery, the intima showed an increase in connective tissue. This connective tissue contained a moderate amount of spindle cells, and was frequently penetrated by thin capillaries. Its nuclear content was enriched by infiltrations of lymphocytes and plasma cells. On its inner surface there was a small amount of fibrin with beginning organization. The elastic tissue played a rather inferior rôle here. The media was demarcated by several layers of elastic fibers. A closed layer of elastic tissue parallel to the intimal surface separated the layer of fibrin and the adjacent connective tissue which probably produced the organization, from the rest of the thickened intima. The former was totally free from elastic elements, while the later was frequently penetrated by delicate elastic fibers. Fresh thrombotic layers more solid and more irregular and rich in blood were superimposed on some parts of the intimal surface (fig. 3).

At the site of the humplike intimal thickenings which appeared macroscopically as yellow nodules with grayish transparent bases, a most complete type of necrosis was noted. These areas were granular, streaky, homogeneously or irregularly colored by eosin, and in places still showed karyorrhectic or round small pyknotic nuclei. Toward the medial side were seen the lumina of tensely filled capillaries (fig. 3).

The elastic stain frequently revealed small heaps of elastic elements partially breaking up. These were irregularly disposed, but seemed to predominate near the media. Between areas of this kind and the media a noncharacteristic type of granulation tissue was interposed, which seemed to be a continuation of the granulations from the media itself (fig. 3).

The Levaditi stain was negative for spirochetes.

A cross-section through the thrombosed right branch of the pulmonary artery or through the main branches which supplied the upper and lower lobes showed that the media was preserved intact throughout its whole extent. The picture in all parts was that of a completely closed recanalized thrombus. The lumen was filled with a rather poorly cellular connective tissue containing numerous prominent vessels, partly of venous and partly of arterial character, many of which showed endarteritic and endophlebitic changes. The loose connective tissue itself in places contained abundant thin elastic fibers in rather dense clusters. Neither in the adventitia nor in the mass of connective tissue filling the original lumen were there cell masses of inflammatory nature (fig. 7).

The small veins in the parenchyma of the lung were filled with blood and sometimes with recanalized thrombi. Masses of connective tissue enclosing small blood vessels were seen in cross-sections of the right lung (fig. 8).

Besides severe fragmentation of the muscle fibers, the heart frequently showed smaller fibrous, scarlike areas poor in nuclei. The sudan stain showed no particular fat content of the heart muscle.

SUMMARY

1. Syphilis of the pulmonary artery, as shown by those cases in which there is no doubt about the etiology, attacks almost exclusively the main trunk and only occasionally extends to one of the main branches. It is a rare disease, not only when considered by itself, but also as compared to the relative frequency of aortic syphilis. Only twelve absolutely certain cases inclusive of the one reported here could be gathered from the international literature studied (group 1).

2. Besides those cases which may be designated as primary syphilis of the pulmonary artery, there is a form which may be called secondary and which is characterized by the immediate extension of gummatous processes from the mediastinum into the wall of the pulmonary artery (group 2).

3. On microscopic examination, the presence of gummas in the trunk of the pulmonary artery exceeds that in the corresponding form of the productive syphilitic aortitic type in the ratio of 9:3. In syphilitic disease of the aorta the proportion is reversed, as far as could be judged from the material so far studied.

4. The forms of syphilis of the pulmonary artery corresponding to the productive aortitis in the material studied are combined with the formation of aneurysms.

5. Gummas of the pulmonary artery may be solitary or multiple. Sometimes they are in the form of a totally diffuse, severe gummatous inflammatory process, as in the case reported here, and may be combined with scarlike changes of the arterial intima, which may result in a closure or thrombosis of one main branch of the pulmonary artery (this case).

6. The formation of gummas in the pulmonary artery, especially in the case of solitary gummas, may cause no change in the lumen. In other cases stenosis results (cases 1, 2, 3, 4, 12). Gummas of the pulmonary artery are frequently accompanied by aortic syphilis, namely, syphilitic aneurysm of the aorta.

7. Frequently the heart participates in the formation of gummas in syphilis of the pulmonary artery. Accompanying syphilitic changes in the other organs, such as gummas or scars in the liver, are not infrequent.

However, the aorta, the heart and the other organs may be found free from the syphilitic processes in the most severe type of syphilis of the pulmonary artery.

8. The necrotic gummatous formations of the severest type may remain entirely localized to the intima of the pulmonary artery. This is contrary to the observations so far described in the pathologic anatomy of gummatous aortitis in that in the latter there is a total syphilitic mesa-ortitis.

THE PRODUCTION OF MALIGNANT ULCERS IN THE SKIN OF RATS

WITH NOTES ON THE CAUSE OF CANCER IN THE UTERUS, BREAST AND LIVER*

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In another article [1] it was shown that sarcomas may be developed from embryonic tissue by treating fragments of this tissue with a Berkefeld filtrate of a Jensen sarcoma of rats. In these experiments it became of interest to see if carcinomas might be developed by the same or a similar procedure, and to study the conditions which led to the development of carcinomas in the adult animal. Previous experiments [2] showed that the response of any tissue to stimulation is proportional to its cell density. In the tissue culture, the cells that grow in fragments placed in plasma or in plasma containing active stimulating substances are those that are more numerous and most compact in the fragment; the other, less crowded, cells are destroyed by the more actively growing ones. Fragments of mesenchyme stimulated to grow in the cultures develop a sarcomatous organization. A few of these fragments transplanted to the animal develop into sarcomas. In the same manner, it was also shown that fragments of the ureter and other tissues containing dense masses of epithelial cells develop into typical carcinomas when stimulated in the cultures. The more densely cellular masses of epithelial cells grow in these fragments at the expense and destruction of the less densely cellular connective tissue and muscle.

In other studies [3] of the behavior of the epithelial and the connective tissue cells in the tissue cultures, it was noted that the conditions that regulate the growth of one of these kinds of cells are not different from those that regulate the growth of the other. Both can grow independently in plasma only when they are crowded into suffi-

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*Burrows, M. T.: The Experimental Production of Malignant Ulcers in Rats, J. Missouri M. A. **20**:145, 1923.

1. Burrows, M. T.: The Production of Malignant Sarcoma in Embryonic Tissue By Means of Berkefeld Filtrates of the Jensen Sarcoma of Rats, Arch. Path. **4**:168, 1927.

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ciently dense masses and in a sufficiently small amount of stagnant mediums well supplied with oxygen The only striking difference between the two types of cells is that the epithelial cells liberate an active proteolytic ferment under the proper conditions. This ferment dissolves the fibrin of the plasma clot. The presence of this ferment often changes the environment about the epithelial cells so that they appear to behave differently from the connective tissue cells, even under otherwise similar conditions.

These facts led to the belief that the tendency for the development of sarcomas in the early life of the animal and of carcinoma in later life is to be related to the relative density of these cells in the different periods. In the early periods of life this same mesenchyme becomes reduced in most parts of the body to cells widely separated by intercellular substances. At this period these cells are concentrated only in the periosteum of bone, in the membranes lining the body cavities and in the ovary. Sarcomas of later life are restricted largely therefore, to these three regions. In other regions the more densely cellular masses are epithelial.

While it seemed most likely that this factor of cell density is important in determining whether a carcinoma or a sarcoma will develop in the animal under the influence of stimulation, a more careful study of the experiments here outlined indicates that this may not have been the most important factor in determining the development of the sarcomas reported in another paper.[1] The embryos used in these experiments were chopped into numerous small fragments, many of which were composed entirely of densely packed mesenchyme cells. Other fragments, such as those of the brain, liver and other organs, were composed almost entirely of epithelial cells. The latter masses of epithelial cells responded by an active growth in the presence of the sarcoma filtrate. There is also no evidence that the epithelial cells do not respond as quickly as the mesenchyme. In fact, they often respond more quickly in the cultures. The development of the sarcomas in these experiments was probably due to a factor not active in tissues left undisturbed in the host. The fragments of the embryo composed largely of epithelium will not attach themselves readily to the host, while the fragments composed largely of mesenchyme become connected readily. Even if the lesions became carcinomas, it was possible that the carcinomas always disintegrated from the lack of this attachment or of a proper blood supply. The untreated fragments of liver, brain and other epithelial organs of the embryo do not grow readily when transplanted into the tissues of the host. As noted in another paper,[1] only part of the fragments of an embryo grow when transplanted into the tissues of the host. The fragments that take are those rich in mesenchyme cells, such as the

skin, intestines, bone, cartilage and sex glands. As also noted in the previous paper,[1] the blood vessels of the host do not grow into a transplanted fragment. For these fragments to take, their blood vessels must grow out and unite with similar sprouting vessels from the adjacent tissues of the host. Investigation of the conditions under which the capillary sprouts can grow out from the transplant and from the host tissues has shown that they can grow only into the fibrinous exudate that connects the transplanted fragment with the host tissues. They move out into the coagulated exudate which accumulates about the transplanted fragment and primarily cements or fastens it to the host tissues. As the endothelial cells enter this exudate they precipitate the fibrinogen to true fibrin and exert tension on the clot. Fibrin fibrils are thus caused to form between the transplant and the host tissues, and the capillary sprouts move along these fibrils. The capillary sprouts of the two sides are thus brought together. As noted previously, epithelial cells, especially those of endodermic and ectodermic origin, liberate active proteolytic ferments under the conditions of transplantation. The ferments dissolve or completely liquify these clotted exudates.[4] This is probably the reason that fragments of the normal liver, brain and other organs never grow when transplanted to the host. They degenerate from the lack of blood supply.

It was not surprising, therefore, that carcinomas failed to develop in the experiments here mentioned. For the same reason, one could not expect carcinomas developed in vitro from any tissue to take with any regularity if transplanted to the host. As noted in the foregoing paper,[1] Barta [5] and Maximow [6] had developed carcinomas in fragments of ureter and breast in tissue cultures by treating these fragments with embryonic extract and bone marrow, respectively. Attempts to transplant to animals the carcinomas thus produced in fragments of tissues have not been successful. As the foregoing observations on transplantation of tissues indicate, this failure may have been due not to the fact that these carcinomatous-like changes are not true carcinoma, but merely to the failure of such tissues to transplant readily. To develop carcinomas by the same method, it seemed evident that one must produce them in the animal and from tissues of the host having an already well established blood supply.

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6. Maximow, A., Ueber krebsahnliche Verwandlung der Milchdruze in Gewebskulture, Virchows Arch. f. path. Anat. **256**:813, 1925.

In the study of the production of sarcomas in the fragments of embryonic tissue, it was found that the sarcomas had developed not from any evident proliferation and continuous action of the stimulus, but from a preliminary transformation of the embryonic fragments from a cellular tissue rich in blood vessels to a similar cellular tissue with a relatively poor blood supply. The stimulus had acted for the time that it had been held in contact with the fragments. During this time it had caused the cells at the periphery of the fragment to grow actively at the expense of the other cells and structures in the fragment. Sarcomas had developed in those fragments in which the cells had become increased and the blood vessels reduced to a certain minimum at the time when they became connected with the tissues of the host. It became of interest in these experiments to ascertain whether carcinomas might be developed in the adult skin of the host by the same procedure.

It has been noted that the tissue of young embryos grows readily after a latent period of a few hours when placed in a tissue culture in which plasma is used as a medium. Adult tissues do not behave the same, however. The adult cells will not grow from cellular fragments in a simple body medium unless they are first washed carefully with plasma over a period of from two to several days.[7] These tissues contain large quantities of growth inhibitor My previous studies [8] indicated that the plasma removes a lipoid substance, the ergusia, from these tissues. This is evidently the active substance that must be removed before the cells can grow independently. It became evident, therefore, that before carcinomas could be made to develop in the adult skin this growth inhibitor must be removed from about the cells. In proof for this belief, I have found that the tissue of malignant sarcomas of rats differs from the normal tissues of rats in that it is free from demonstrable ergusia or growth inhibitor. The actively growing embryonic tissue, on the other hand, contains small quantities of this substance.[9] As is evident, therefore, the formation of the sarcomas reported in the previous paper [1] must have been due not alone to the crowding of the cells, but also to the removal of this small quantity of the growth inhibitor. How this small quantity of growth inhibitor had been removed from these embryonic tissues in transforming them to sarcomas also became a problem of interest in this further analysis of the subject.

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7. Lambert, R. A.: Comparative Studies Upon Cancer Cells and Normal Cells: II. The Character of Growth in Vitro with Special Reference to Cell Division, J. Exper. Med. **17**:499, 1913.

8. Burrows, M. T.: The Mechanism of Cancer Metastasis, Arch. Int. Med. **37**:453 (April), 1926.

9. Burrows, M. T., and Jorstad, L. H.: On the Source of Vitamin B in Nature, Am. J. Physiol. **77**:24, 1926.

It was noticed in a few of the experiments reported in the previous paper [1] that when fragments of embryonic tissue were placed in the derm of the host rather than in the subcutaneous tissue, they caused atrophy of the epidermis, and a great loss of blood vessels and hyalinization of the surrounding derm. It became of interest to see, therefore, whether this atrophy and loss of blood vessels in the skin of the host could be related in any way to the loss of the ergusia, or the growth inhibitor, in these tissues.

It is well known that spontaneous cancers of the skin in man arise either in cellular benign tumors or in parts undergoing atrophy. There is also much evidence to show that a similar atrophy precedes the development of cancers in other parts of the body. Chronic inflammatory processes with hyaline changes and atrophy precede the development of cancers of the breast in most, and perhaps in all, cases. The same is true probably for cancer of the uterus. Either leukoplakia or chronic inflammation most often precede the development of cancers of the mouth. Primary cancers of the liver have not been seen in other than cirrhotic livers.

While this relation between atrophy and cancer is well known, it is equally well known that not all tissues that undergo atrophy become cancerous. Whether this latter fact indicates that the atrophy must have reached a certain amount before cancers develop or whether the atrophy is only one of two or numerous factors causing this disease had not been determined. It became of interest, therefore, to study these atrophies and their possible relation to the general conditions necessary for the independent growth of the normal cells of the body as noted by the studies of the tissue cultures.

Cancers of the skin of man occur most frequently in persons exposed to weather, light or other specifically acting conditions and substances such as coal tar and other lipoid solvents. They do not tend to occur in all parts of the body of these persons, but only in those areas exposed to light or to the other specifically active substances. In farmers and sailors, cancers appear most frequently on the face and hands. Cancers of the scrotum are common in chimney sweeps. In engineers and firemen, cancers are common on the parts of their legs that are more or less continuously exposed to the glare of the fire box of the engine. The roentgen ray also causes similar changes in the skin and cancer in persons exposed to it.

Since these experiments were completed Jorstad [10] has shown that the primary action of coal tar is atrophy and hyalinization, and as I have

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10. Jorstad, L. H.: The Action of Lipoid Solvents on the Organism and in the Production of Cancer, J. Cancer Research **10**:229, 1926.

proved, this atrophy and hyalinization is the result of the removal of the ergusia from the tissue.[11] I have also shown that light acts in a similar manner.[12] Since it is well known that many cancers peculiar to man arise from other conditions and apparently largely independent of such causative agent, it became of interest to see whether an actively growing tissue might not also bring about similar changes in the tissue. Many of the cancers of the breast and uterus are difficult to explain, except in terms of the more or less continuous stimulation these organs suffer in the course of normal life.

In the light of these facts, I began to study the atrophies produced by the growing embryonic tissue which had been placed in the derm of a few of the animals, and to study them more carefully in terms of the general facts referable to an independent growth of cells, as deduced by the tissue culture.

EXPERIMENTS

Two sets of these experiments were planned and performed. In the first series of experiments from 0.3 to 0.4 Gm. of untreated fragments of 13, 14, 15 or 16 day old rat embryos, respectively, were injected into the derm of the skin of young rats that were full brothers and sisters of the embryos. Sixty-seven rats were used for these first experiments; fourteen received from 0.3 to 0.4 Gm. of untreated fragments of 13 day old rat embryos; nine the same quantity of untreated fragments of 14 day old rat embryos; twenty-three injections of two chopped up 15 day old rat embryos respectively, and twenty-one rats each received chopped up 16 day old rat embryos. The injections were made into the dermis, directly beneath the epidermis. The fragments were cut small so as to be introduced through a small hypodermic needle. These fragments grew the same as those injected into the subcutaneous tissue (fig. 1). Atrophy of the epidermis with loss of hair appeared eventually in all of these cases. In many it appeared as early as from ten days to two weeks after the embryonic tissue had been transplanted. This early appearance of atrophy was more common in those rats that had received injections of the fragments of older embryos than in those that had received injections of fragments of the younger embryos. It progressed always to

11. Burrows, M. T.: Energy Production and Transformation in Protoplasm As Seen Through a Study of the Mechanism of Migration and Growth of Body Cells, Am. J. Anat. **37**:239, 1926; The Nature of Hyalinization and Atrophy in Cells and The Tissues, to be published. Studies on the Nutrition of Tissue Cells, to be published.

12. Burrows, M. T.; Jorstad, L. H., and Ernst, E. C.: Cancer, Vitamin Imbalance and Roentgen-Ray Activity, J.A.M.A., **87**:86 (July 10), 1926. Further Studies of the Effect of Graded Doses of X-Rays on Animals Fed Various Dietaries, with a Note on the Effect of Dietary in the Treatment of Patients with X-Rays, Radiology, to be published.

the eventual formation of ulcers in the centers of the atrophic areas. In the rats receiving fragments of 13 and 14 day old rat embryos, the ulcers did not appear until sometime between seven and eighteen months after the fragments had been transplanted or the tumors had become large. The ulcers developed in most of these cases when the tumors were between 9 and 15 months old.

Corresponding with this late appearance of the ulcers, the skin also often failed to show atrophy at the beginning of the growth of these younger embryonic fragments. There was, on the other hand, a primary hyperplasia of the epidermis. The hair grew more rapidly in this area, and the epidermis thickened.

When fragments of 15 and 16 day old embryos were introduced this early, hyperplasia either was absent or was of short duration. Atrophy appeared early and progressed to ulceration, generally by the fourth month.

Figure 1

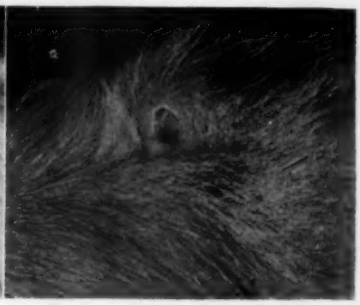

Figure 2

Fig. 1.—A carefully dissected embryoma which developed in the subcutaneous tissue of a rat injected with one chopped up 15 day old rat embryo.

Fig. 2.—An atrophic ulcer, which formed in the epidermis in contact with an embryoma in the dermis of a rat; a cyst of the embryoma ruptured through the ulcerated area; the embryoma developed from the fragments of one chopped up rat embryo, 16 days old; the ulcer developed after four months of growth of the embryoma; the photograph was taken six months later.

Many of the ulcers healed after a time, only to reform again. In several instances, cysts of the embryomas ruptured through them (fig. 2). None of them ever showed any malignancy. Aside from the few removed for histologic study, they were left undisturbed throughout the life of the rats, from one and one-half to two and one-half years. Forty-four such ulcers were left undisturbed during this time. One became infected, and a large abscess formed in the embryoma. Almost the entire embryoma became necrotic. This infection led to the death of the rat. The walls of the abscess cavity in this case showed the characteristic picture of the wall of pyogenic abscesses in these animals.

The other ulcers showed little change, except in size after their formation.

Microscopically these ulcers are of the simplest type. The tissue about them is atrophic and often shows hyaline changes. Cellular or

Fig. 3.—A low power photomicrograph of the edge of one of the simple atrophic ulcers which developed over these embryomas; this cyst is lined with squamous epithelium; atrophic hair follicles and sweat glands are seen in the tissue beneath the ulcerated area.

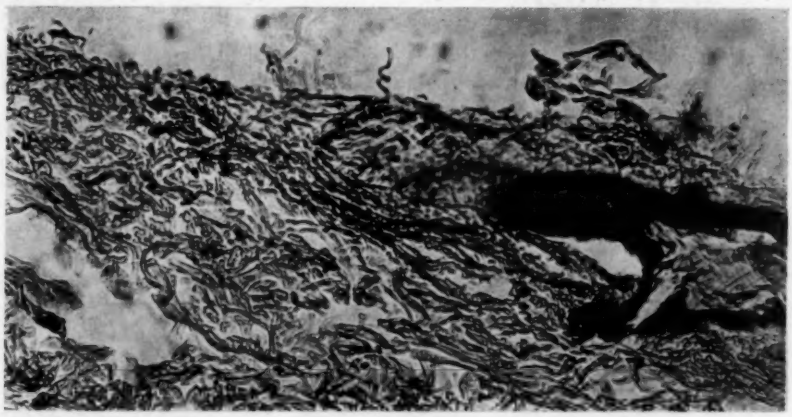

Fig. 4.—A higher power photomicrograph of the edge of the ulcer shown in figure 3; the atrophy and sclerosis of the epidermis after an evident hyperplasia and the general early hyaline changes in the connective tissue of the derm should be noted.

vascular reaction does not take place at the edges and base of the ulcers, and the epidermis ends bluntly at the edge of the ulcer. A poorly cellular and partially hyalinized connective tissue forms the base (figs. 3 and 4).

THE EFFECT OF INJECTIONS OF FRAGMENTS OF EMBRYONIC TISSUE PREVIOUSLY TREATED WITH A BERKEFELD FILTRATE OF A JENSEN SARCOMA

Having failed to produce carcinomas with injections of the untreated embryonic fragments, in the next experiments I was interested to note the effect of a more active growth of this embryonic tissue. In the experiments reported in the previous paper it was shown that a certain number of fragments of 15 and 16 day old rat embryo grow much more actively after treatment with the filtrate of an extract of Jensen sarcoma. In the second series of experiments it was interesting, therefore, to inject fragments of 15 and 16 day old rat embryos first treated with a Berkefeld filtrate of an extract of a Jensen sarcoma. Fragments of 1½ or 2 to 15 day old rat embryos or 1 to 16 day old embryo were injected into each host. Seventy-five animals received injections, not including a few of the earlier experiments. In approximately forty of the animals the embryonic tissue grew fairly well; in six it grew excessively.

In these cases, it is interesting that the fragments did not affect the skin of the host the same as those of the same age embryos that were not treated with the Berkefeld filtrate of the sarcoma. Treatment with the tumor extract changed the fragments of the 15 and 16 day old embryos so that they acted on the skin in most instances the same as untreated fragments of 13 and 14 day old embryos.

As noted previously, the skin suffered an early hyperplasia about the fragments of 13 and 14 day old rat embryos, and then a slowly progressing atrophy proceeding to ulceration after from nine to eighteen months. About the untreated fragments of 15 and 16 day old embryos, this atrophy commenced earlier and proceeded to ulceration much more rapidly. Ulcers generally appeared as early as the fourth month. Treatment with the Berkefeld filtrate of the sarcoma slowed the oncoming atrophy of the host tissues about these older fragments, so that the picture was the same as that about the younger embryonic fragments. The epidermis underwent first a hyperplasia, and then a slow atrophy proceeding to ulceration after from nine to eighteen months.

In one of the rats, however, the picture was different. Injections into the skin of this rat had been made with fragments of one 16 day old rat embryo, these fragments having been previously placed in a Berkefeld filtrate of Jensen sarcoma for seven minutes. In this rat, two ulcers appeared at the end of the fourth month. These ulcers were different from those noted in the other rats of this series. They had a woody hard resistance, thickened, gray, opaque edges and dirty, thick, gray bases. They resembled in every way cancers of the skin as seen in man. Sections of both ulcers showed them to be adenocarcinomas arising from the sweat glands of the skin at the site of the introduction of

the embryonic tissue and the Berkefeld filtrate of the Jensen sarcoma (fig. 5). A section of the other tumor is published (Burrows).[13]

In these experiments, carcinomas developed in the presence of the Berkefeld filtrate of the sarcoma. There was not any possibility that these tumors arose from any cells in the filtered extract of the sarcoma. They arose, evidently, from the sweat glands of the skin of the host. The strain of rats to which the host belonged has been in the laboratory under constant observation for five years. Spontaneous malignant tumors had never arisen in the ancestors of this rat or in any of the other rats in the laboratory. There was no evidence to show, there-

Fig. 5.—A section of one of the malignant ulcers growing in the skin over a four month embryomas which developed from one chopped up 16 day old rat embryo taken up and injected with a Berkefeld filtrate of the Jensen sarcoma.

fore, that these tumors arose from other than the experimental conditions imposed on this rat.

COMMENTS

To produce the sarcomas noted in the previous paper [1] it was necessary to inject the filtrate with fragments of embryonic tissue that could grow in its presence. The filtrate injected alone is without effect. Cancers did not develop when the embryonic tissue alone was introduced. The combination of the two led to the development of the sarcomas.

13. Burrows, M. T.: Is Cancer a True Disease or Merely the Result of a Condition of Change in the General Organization of the Organism? (fig. 3), Radiology **4**:407, 1925.

The carcinomas described in this paper did not develop in the embryomas, but in the adjacent tissues of the host. These tissues had suffered a preliminary hyperplasia and a subsequent atrophy in the presence of the growing embryonic fragments and the sarcoma filtrate.

In the previous experiments [1] considerable evidence has been presented to show that the sarcomas developed as the result of a local stimulation and growth of the cells in the embryonic fragments with a degeneration of other parts. This proliferation does not take place in a manner to build a normal tissue. It leads always to the formation of dense masses of cells free from blood vessels. Other blood vessels of these fragments also suffer destruction during this local proliferation of cells. When the blood vessels are completely destroyed, the fragments degenerate when transplanted to the host. When the vessels are not sufficiently destroyed, the fragments grow normally or more rapidly to form benign embryomas. When the vessels are reduced and the cells increased in the proper proportions, the sarcomas developed. The sarcomas developing in these experiments were explained previously as the result of this change in organization of the tissue. My later experiments have shown, however, that these tissues must have also suffered a decrease in their ergusia content. How this was accomplished was not explained.

In the experiments reported in this paper, it has been shown that carcinomas can be developed in the skin of the host as the result of the same changes in organization. The carcinomas in these experiments developed after a primary stimulation of the epithelial cells or of the more cellular masses of the skin, with a corresponding decrease in blood supply and atrophy of the connective tissue. In both instances, the conditions were the same. The malignancy was directly the result of an increase in certain masses of cells with an atrophy and hyalinization of others and a reduction in the blood supply of the whole.[2] Sarcomas have not been developed so far in the embryonic fragments, except in those cases of stimulation with the Berkefeld filtrate of the Jensen sarcoma. In the same manner, carcinomas did not develop in the skin of the animals that had received injections with the chopped up embryos alone. To produce the carcinomas it was necessary to cause an excessive growth of the embryonic tissues by treating them with the extract of the Jensen sarcoma, and only in the cases in which the embryonic tissue suffered the excessive growth noted in the few experiments of the previous paper [1] did the carcinomas develop.

In again going over the experiments reported in this paper, it was noted also that the sarcomas developed practically at once in the embryonic tissue, while the carcinomas appeared only after a latent period of four months. The differences in the time of development correspond closely to the differences in the time required for these tissues

to respond by growth in the cultures and also to the differences in the ergusia content of these tissues.[9] In previous experiments in the laboratory, it was shown that coal tar and other lipoid solvents act to produce cancer, in that drops of these oils attract the cells away from their intercellular substances and blood vessels and crowd them about their peripheries.[14] These drops of lipoid solvents also cause hyalinization and atrophy of the tissues, which are similar to the precancerous lesions known to man. These changes in the tissues are also comparable to the lesions noted in these experiments and after the use of roentgen rays.

My studies of the mechanism of the migration of tissue cells[15] and of the action of lipoid solvents have shown that the migration of cells toward the drops of the lipoid solvents and the eventual hyalinization of the tissues is the result of a simple dissolving of the ergusia or lipoid soluble elements of the tissues and cells by the lipoid solvents. It has also been shown that roentgen rays act by a slightly different procedure to remove these lipoid soluble elements from the cells and tissues.[16]

While it is impossible without a further analysis of the exact structure and composition of intercellular substances and cells to prove completely that these atrophies and hyalinizations are the result of the simple removal of the ergusia, or the lipoid soluble elements, from the cells and intercellular substances, the analogies between the changes produced by the growing embryonic tissues and the lesions preceding and accompanying cancerous development in the organism are complete. In the papers [17] that follow this one, I have made these analyses and have shown not only that the removal of the ergusia must produce these hyaline and atrophic changes in the cells and tissues, but that the ergusia is also absolutely essential for the growth of the tissue cells.

The studies of coal tar and roentgen rays indicated clearly that these substances act to produce in the tissues the same changes necessary for an independent growth of body cells in the tissue culture. They induced the cancers either by dissolving the excess of the ergusia and causing the cells to move together into stagnant masses so that they could form and retain ample archusia (S) for this growth, (this is seen in the action of oils and tar) or by destroying the blood vessels and mobilizing the fat soluble vitamin fractions of the tissues so that they were removed from the tissues affected by other normal tissues of the organism (this is shown in the action of roentgen rays and radium).[16]

As is well known, however, cancers may be induced not only by lipoid solvents, roentgen rays and radium, but also by animal parasites

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14. Jorstad, L. H.: The Behavior of Coal Tar in Adult and Embryonic Tissue, J. Cancer Research **9**:232, 1925. Burrows and Johnston (footnote 2).

15. Burrows (footnote 11, first reference).

16. Burrows (footnote 12, second reference).

17. Burrows (footnote 11, second and third references).

(Febiger) [18] and by bacteria (Smith).[19] The striking frequency of cancers of the breast and uterus of women is also difficult to explain in terms of any facts so far deduced. While a common precancerous lesion of the breast (chronic cystic mastitis) has been classed with chronic inflammation, it is peculiar in that the prominent changes in this condition are hyaline changes in the vessels and connective tissue and hyperplasia of the epithelium. It is also questionable whether any evidence has been established in favor of chronic irritation playing a necessary rôle in the development of cancer in either the uterus or the breast. It is interesting to note in this regard that the women who have the most children and who suffer the most injuries to their breasts are not the ones who have cancer. Early breast cancer is most common in women who have not suffered such injury. Cancer develops in the uterus or breast that is undergoing generalized or localized vascular changes and hyalinization of the intercellular substances. While it is well known that acute and chronic inflammations precede the development of these cancers in many cases, these absolutely proved forms of inflammation do not precede all cases. As I have pointed out elsewhere,[20] chronic cystic mastitis resembles chronic interstitial nephritis, the leukoplakias and kraurosis. These latter lesions are similar to those produced by coal tar, other lipoid solvents and roentgen rays, burns from excessive heat and the atrophies and hyaline changes in the skin following continuous and long exposure to the sun's rays, or artificial lights containing ultraviolet rays. Since Hartman, Bollinger and Doub [21] have shown that a typical chronic interstitial nephritis can be produced by injuring the kidneys with roentgen rays, one is justified, as I have noted,[20] in placing such lesions as chronic interstitial nephritis, chronic cystic mastitis and certain of the liver cirrhoses in a class with the leukoplakias and other precancerous lesions, rather than in that with chronic infectious inflammations.

Evidently, then, before any conclusions can be drawn about the cause of cancers of the breast and uterus, one must analyze in detail the various peculiarities of these organs and all the factors involved in their normal functions. Primary cancers of the liver have not been observed, to my knowledge, except in cirrhotic livers. I have seen primary can-

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18. Febiger, K.: On Spiroptera Carcinomata and Their Relation to True Malignant Tumors, With Remarks on Cancer Age, J. Cancer Research **4**:367, 1919.

19. Smith, E. F.: Studies on the Crown Gall of Plants, Its Relation to Human Cancer, J. Cancer Research **1**:231, 1916.

20. Burrows, M. T.: Functional Studies Throughout the Course of Roentgen-Ray Nephritis in Dogs, J. A. M. A. **88**:857, 1927.

21. Hartman, F. W., Bollinger, A., and Doub, H. P., Functional Studies Throughout the Course of Roentgen-Ray Nephritis in Dogs, J. A. M. A. **88**:139 (Jan. 15), 1927.

cers of this organ in Banti's cirrhosis, as well as in the so-called alcoholic cirrhosis. In both of these types of cirrhosis, the liver often suffers for a long time not only degenerative changes but also active regeneration. The animal parasites and bacteria that induce cancer in animals and plants liberate growth stimulating substances. They induce an active growth of the neighboring cells of the host. To understand the manner in which these parasites produce cancer, one must understand the effect of such a growth of cells of the host on the surrounding normal tissues of the host as well as on these growing cells themselves.

One of the peculiarities of cancer of the breast and of the uterus in women is their great frequency. A difference in the habits of the modern man and the modern woman is a tendency on the part of the latter to starve herself, whereas the man does not. The foods that women shun most are the fattening ones, such as milk, cream, butter and eggs. A striking peculiarity of the breast and uterus of women is that they suffer periodic stimulation and growth. These periods of growth coincide with the ovarian cycles or menstrual periods. Before any conclusions were drawn in regard to the cause of the frequency of breast and uterine cancer, it seemed necessary to prove or disprove, therefore, that such cycles of growth might not be important for the induction of these cancers. It was also equally important to know, if such cycles of growth are important, why they are not operative in more women than they are.

The experiment reported in the previous paper [1] answers these questions. It was possible to show that an actively growing tissue may induce a loss of blood vessels and hyaline changes in adjacent tissues. When stimulated by the Berkefeld filtrate of the Jensen sarcoma the same actively growing embryonic tissue caused not only the atrophy and hyaline changes but also a true cancerous process. This cancerous transformation does not take place except when the growth of the embryonic tissue is stimulated with a tissue extract free from ergusia, but rich in archusia. Even traces of the ergusia in the extracts of young embryonic tissue prevented the cancerous transformations.

When cancer of the breast is considered with these facts in mind, one notices that the epithelial cells suffer the periodic growth changes. Preceding the development of cancer in the breast, the connective tissue portions suffer atrophic and hyaline changes; the fat disappears, and the blood vessels are obliterated, and the epithelial cells either proliferate to form extra layers which fill the alveoli or ducts, or grow to form cysts. As this hyperplasia of the epithelium and the degeneration of the connective tissue continues, cancers eventually develop.

The experiments reported in this and in the previous paper [1] were performed on well nourished and well fed hosts. My work on the action of coal tar [14] and roentgen rays [18] has shown definitely that dietary is most important in effecting these changes. The removal of

the ergusia with hyaline and atrophic changes and cancer—the uses of coal tar or roentgen rays—is accelerated in underfed animals and greatly hindered in animals receiving a well rounded dietary high in vitamin A. There is not any reason to believe, therefore, that the presence of a cancer of the breast or uterus in one woman and not in another may not be related to her food intake and her hereditary or acquired ability to use this food.

In further proof for this deduction, it is important that an oil tumor in the arm of a woman suffering from chronic interstitial nephritis became active and grew at once when she placed herself on a vitamin-free dietary, and returned to its previous size and quiescent state on a vitamin-rich dietary.[22]

In the same manner, these experiments indicate that any actively growing bacteria or animal parasite that can stimulate growth in the cells of the host may induce cancer. My analysis of the action of *Pseudomonas tumefaciens* has shown that it liberates only vitamin B during its active periods of growth. Its actions on animals fed with it is exactly the same as that of the Jensen sarcoma. In plants in which this organism grows readily, the tissues must suffer those same changes observed in the embryonic tissue treated with the Berkefeld filtrate of the Jensen sarcoma.[1] The tissues surrounding these cells stimulated to grow by the parasites must suffer changes identical to those about the growing embryonic tissues. The same applies to the action of the animal parasites described by Wood and his assistants[23] and by Febiger.[18]

In the light of these facts, primary cancer of the liver may be also the normal outcome of cirrhosis of the liver in any person surviving for a sufficiently long time. The continuous regeneration of liver tissue in this process must eventually reduce the vitamin A content of the liver to that point necessary for an independent growth of its cells.

Possibly, therefore, by these experiments, an explanation has been found for cancers of the breast and the uterus, which explains their frequency and their existence in terms of the facts known about them. The same applies to primary cancer of the liver, and probably can be shown to be important in the development of cancer in other internal organs. One should not expect renal cancer to develop when both kidneys are involved with a chronic interstitial nephritis. These organs are too essential to the life of the person. Cancer should develop only when the change occurs in a small area or areas of either kidney.

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22. Burrows, M. T., and Jorstad, L. H.: The Cause of the Growth of Sarcoids or Oil Tumors, J. A. M. A. **88**:1460, 1927.

23. Bullock, F. D., and Curtis, M. R.: The Experimental Production of Sarcoma of the Liver of Rats, Tr. N. Y. Path. Soc. **20**:149, 1920.

CONCLUSIONS

1. Untreated rat embryonic tissue injected into the derm of the skin of host rats grows actively and produces atrophy and ulceration of the host's tissue. While the younger embryonic tissue grows more actively, it produces the atrophy and ulceration more slowly than the tissues of older embryos.

2. The addition of a Berkefeld filtrate of a Jensen sarcoma to the older embryonic tissue causes a marked slowing in the appearance of atrophy and ulceration in the adjacent host's tissues.

3. Carcinomas have not developed in the animals that received injections of the untreated embryonic tissue. Carcinomas have developed only in a limited number of these animals that received injections of embryonic fragments taken up in the Berkefeld filtrate of the Jensen sarcoma.

4. The fragments of tissue of older embryos produce ulceration of the skin after about four months. The addition of the Berkefeld filtrate to these fragments delays this development of ulceration so that it does not appear until after from nine months to a year and a half. The carcinomas in these cases appeared about four months after the injection of the tissue.

5. The development of the carcinomas in these cases can be explained as the result of the removal of the ergusia or vitamin A[24] from the tissues, a stimulation of the cells of the host with an associated disappearance of the blood vessels. The cancers have been shown to result, therefore, from changes that are produced by coal tar, other lipoid solvents, roentgen rays and other conditions leading to cancer.

6. Cancers develop only when extracts of tissue rich in the archusia and poor in the fat soluble vitamins are used for stimulation. Even traces of fat soluble vitamins prevent the cancerous production.

7. Cancers of the breast and the uterus in the undernourished woman may be only the result of the normal periodic stimulation that the epithelium of these organs suffers.

8. Primary cancer of the liver may be explained as the result of the regenerative and degenerative changes peculiar to cirrhosis of the liver.

9. Animal parasites and bacteria cause an active proliferation of the host cells which, in turn, must lead eventually to cancer.

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24. The term "vitamin A" has been used in the several papers not, in the sense of many recent chemists, to designate one of the fat soluble vitamins, but to designate all of those fat soluble vitamins necessary for normal growth.

Laboratory Methods and Technical Notes

EFFECT OF BLOOD PRESERVATIVES ON UREA DETERMINATION*

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The value of a mixture of 0.001 Gm. thymol and 0.01 Gm. sodium fluoride, first suggested by Sander [1] as a preservative for specimens of blood for chemical analysis, has been substantiated by numerous workers. The efficiency of this preservative in inhibiting glycolysis has led to its wide use in blood sugar determinations.

Effect of Blood Preservatives on the Urea Determinations

	Oxalate Filtrate			Fluoride Thymol Filtrate		
Case	Urea Nitrogen	Nonprotein Nitrogen	Creatinine	Urea Nitrogen	Nonprotein Nitrogen	Creatinine
1	137	...	11	10	...	11
2	20	50	2	11	50	2
3	18	36	1.7	8	36	1.7
4	17	...	...	5	...	...
5	100	...	4.5	67	...	4.5
6	21	...	...	5	...	...
7	10.2	...	...	5	...	...
8	15.6	...	...	9	...	...
9	60	...	...	10	...	...
10	100	255	11	50	255	11
11	140	200	9.5	14.5	200	9.5
12	150	270	10.5	12	270	10.5
13	83	180	9	16	180	9
14	11.3	...	...	4	...	...
15	129	225	7	45	225	7
16	17	...	1.2	5	...	1.1
17	140	240	9.5	40	240	9.5
18	140	195	9	35	195	9
19	11.2	36	1.25	4	36	1.25
20	12	33	1.1	5	33	1.1

Because the mixture, which is an anticoagulant as well as a preservative, sometimes is used in specimens intended for general analysis by the Folin-Wu technic, it is of practical importance to note that it markedly affects the values obtained for urea. This effect is well shown in the accompanying table.

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1. Sander, F. V.: J. Biol. Chem. **58**:1, 1923.

While Schwenker [2] has stated that the sodium fluoride preservative is without effect when the system of analysis outlined by Myers [3] is used, in which the aeration technic is employed for the determination of urea, it is obvious from the table that erroneous results will be obtained when any method other than aeration is employed for this purpose.

RAPID HISTOLOGIC METHOD FOR ZENKER-FIXED TISSUE*

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The pathologic laboratory is often requested to "rush" certain specimens, so that a report of a histologic examination can be ready in about twelve hours. The frozen section method has its obvious limitations, and there are various methods for formalin-fixed tissue for rapid work. Zenker's fluid is the best all round fixative known today, and at the Albany Hospital the following method has been used satisfactorily for several years. It permits paraffin sections of Zenker-fixed tissue to be reported on in ten hours. Complete fixation, of course, depends on whether the fluid is sufficient for the amount of tissue. It is our practice to use a piece 2 by 2 by 0.2 or 0.3 cm. in from 80 to 100 cc. of fixing fluid.

The following steps are then observed:

1. Fix in Zenker's fluid for three hours.
2. Wash three hours. (This usually removes all bichromate, but no harm is done if a trace remains, as it will be removed by washings of the section.)
3. Place in 80 per cent alcohol for one half hour.
4. Place in 95 per cent alcohol for one half hour.
5. Place in absolute alcohol, one half hour.
6. Place in second absolute alcohol, one half hour.
7. Chloroform, one half hour.
8. Saturated solution of paraffin in chloroform, one half hour.
9. Place in oven for ten minutes.
10. Embed at 53 C. for from twenty to thirty minutes.

Cutting and staining is done as follows:

1. Cut sections and mount on slide by albumin-glycerin method.
2. Place slide in an upright position in oven for twenty minutes.
3. Draw slide over edge of a hot plate several times to assure secure mounting.
4. Chill by holding slide on ice, and blot. (Steps 3 and 4 occupy five minutes.)
5. Place in xylol for five minutes.
6. Dip into absolute alcohol. Dip into 95 per cent alcohol. Dip into 80 per cent alcohol.

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* From the Pathologic Laboratory of the Albany Hospital and Department of Pathology of Albany Medical College.

2. Schwenker, F. F.: Preservation of Blood for Chemical Analysis. Arch. Path. **3**:410 (March) 1927.

3. Myers, V. C.: Practical Chemical Analysis of Blood, ed. 2, St. Louis, C. V. Mosby Company, 1924.

7. Place in 0.5 per cent iodine for five minutes.
8. Decolorize in four changes of 80 per cent alcohol.
9. Delafield's hematoxylin from ten to fifteen minutes.
10. Acid alcohol to remove any excess of hematoxylin. Wash in water. (Usually there is no excess of hematoxylin, and this step is unnecessary.)
11. Restore hematoxylin blue with weak ammonia water. Wash in water.
12. Place in eosin or phloxine; then in absolute alcohol; then in xylol.
13. Mount in xylol balsam.

General Review

ACUTE YELLOW ATROPHY OF THE LIVER*

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INTRODUCTION

General Comment.—Acute yellow atrophy of the liver is a well characterized anatomic condition which presents in typical cases a picture that is unique in pathology, nothing similar occurring in any other organ. The accompanying clinical manifestations are common to a large group of infections or intoxications involving severe damage to the liver, with jaundice as a prominent symptom and often spoken of as icterus gravis. Therefore, as the important feature of the condition is a rapid reduction in the size of the liver, the diagnosis will depend on the clinical demonstration of that phenomenon. In other words, acute yellow atrophy is an anatomic but not a clinical entity. The etiology is unknown, but many cases of poisoning with different substances such as phosphorus or chloroform have led to changes in the liver identical with those of acute yellow atrophy. In contradistinction to such cases, the acute yellow atrophy of unknown etiology is often designated as "genuine," "primary," "idiopathic" or "cryptogenic." The cryptogenic variety will be the center of discussion in this review.

Name.—Acute yellow atrophy is a time-honored name, but I shall show that the pathologic condition which it is supposed to designate frequently justifies neither the term "acute" nor "yellow," and occasionally it may not even justify the term "atrophy." The unfitness of the name is universally recognized, but as it is no longer taken literally its use is generally continued, and is therefore used in this article, the word yellow often being omitted for the sake of brevity. There seems to be little advantage in coining new names such as "acute necrosis," "acute autolysis," "hepatic dystrophy," "heptolysis," etc., for a condition in which the nosologic position is uncertain and the etiology obscure.

Early History.—If the subject of acute yellow atrophy is approached from the anatomic side, its history begins with Rokitansky[1] (1842), who first described it as a specific disease that was well characterized anatomically in relation with the symptom-complex of icterus gravis (icterus typhoides). Previous to this, a case of what seems to have

* From the Buffalo General Hospital.

1. Rokitansky, C.: Handbuch der pathologischen Anatomie, 1842, vol. 3, p. 313.

been acute yellow atrophy of the liver is recorded by Abercrombie (1821 ?), under the name of black ramollisment of the liver. A woman, aged 50, was suddenly seized with deep jaundice and nausea, but no fever or other complaint. Afterward, frequent vomiting of black matter set in, and death occurred after an illness of about three weeks. At necropsy, the liver appeared reduced to one third of its natural size; it was dark, extremely soft and apparently disorganized. The gallbladder was empty and collapsed. This case is reviewed by Budd [2] (1846), who in addition gives full details of the reports of two cases published by Alison (1835) and two by Bright (1836), all with necropsies, which could well have been acute yellow atrophy.

At least one of the cases of fatal jaundice reported by Morgagni [3] (1760) is probably one of acute yellow atrophy. The patient was a young priest who was seized with "the jaundice a little after a kind of perturbation of the mind." This was associated with pain in the epigastrium and vomiting of dark material. After a day or two stupor set in, followed by delirium. Blood drawn from a vein yielded a serum that was tinged yellow. The convulsions then ceased, and the patient lay in a stupor. There was no fever, and respiration was almost natural. Death occurred at the beginning of the fifth day. At necropsy the liver was found "flaccid and inclining to a palish color." In the gallbladder, there was a darkish bile. The inner lining of the stomach showed multiple punctate hemorrhages.

Possibly also two of the several cases of grave icterus included in the Sepulchretum of Bonnet have been cases of acute yellow atrophy. The one refers to an observation of Ballonius [4] of the case of a boy, aged 14, who, on the fifteenth day of a simple icterus, showed violent cerebral symptoms which rapidly led to his death. At necropsy, nothing remarkable was found in the brain, but the liver was "peculiarly discolored." The other report, an observation of Guarinonius,[4] is of a case in which the patient (Cardinal Sforza) died on the sixteenth day of his jaundice; the last three days of the illness were associated with violent convulsions. At necropsy, the liver was yellow, and the blood was everywhere black and fluid.

The reference to Franciscus Rubeus (1660) as possibly being the first to report a case, as claimed by Lebert [5] or Thierfelder,[6] seems questionable. The patient was a man, aged 22, who after suffering from

2. Budd, G.: Diseases of the Liver, Philadelphia, Lee and Blanchard, 1846, chapter 3, p. 198.

3. Morgagni, J. B.: De sedibus et causis morborum **2**:212 (letter 37, article 2), translated by B. Alexander, London, 1760.

4. Cited by Morgagni (article 6).

5. Lebert: Ueber Icterus typhoides, Virchows Arch. f. path. Anat. **7**:343, 1854.

6. Thierfelder: Handbuch der speziellen Pathologie und Therapie, von Ziemssen, ed. 2, 1880, vol. 9, p. 212.

a simple icterus for four days, developed violent delirium, passed into coma, and died on the next day. There is no record of a postmortem examination.

The credit for the first demonstration of a destructive process in the liver cells by the aid of the microscope is due to Busk[7] (1846), an English physician whose observations were confirmed by Budd.

A good survey of the anatomic picture can best be obtained from the classic description of Rokitansky. The following is a literal translation of the original quoted by Eppinger:

> The liver appears collapsed to one-half or one-third of its normal volume, and is especially strikingly reduced in its thickness, and with it all extraordinarily flabby, mushy, even diffluent, and thoroughly saturated yellow in color, its granulations obliterated. The bile vessels and the gallbladder contain little dark brown, dark green, viscid bile, mostly a mucobiliary secretion. The blood vessels contain a dark, cherry-red, dirty brown-red blood. Closer examination shows disintegration of the liver cells to a finely granular detritus; the cells are cloudy, collapsed, and going into solution, disappearing finally and giving place to the detritus with which are mixed fat globules in varying quantity, bile pigment, crystals of tyrosin and leucin. Frequently fat is present partly in globules of considerable size in strikingly large quantity. To these findings are added the further phenomena of icterus, ecchymoses and blood suffusions of the tissues (peritoneum, omentum, mesentery, pleurae, mediastinum, pericardium, myocardium, endocardium, kidneys, pelves of the kidneys, tracheal mucosa, etc.) and hemorrhages including intestinal and uterine hemorrhages, wetness and swelling (edema) of the brain, hypostasis of the lungs, weakening, mushiness, and yellow coloration of the heart muscle, dark-red splenic tumor, hemorrhagic erosion of the gastric mucosa, gray bile-free bloody tarry intestinal contents, swelling or collapse, flabbiness, intense icterus of the kidneys with sparse cloudy icteric content of the urinary bladder; anemia, lack of fibrin, dark brown-red, cherry-red fluid, blood, gluey blood masses.

It was on the basis of these observations that acute yellow atrophy established itself as a pathologic entity, though not without considerable controversy (Lebert, Buhl,[8] Förster[9] and Rokitansky).

Thirty years later, Zenker[10] (1872) reported some cases of acute atrophy of the liver in which the organ, particularly the left lobe, instead of being yellow, showed a bluish-red color, was much more shrunken and tougher than the yellow-colored right lobe and on cut surface was smooth, the parenchyma not bulging, though with equally obliterated markings. Here, then, the atrophic liver was red instead of yellow, and the question arose whether the red atrophy is merely a further stage, as held by Zenker, or an independent condition, as held by Klebs.[11]

7. Busk: Cited by Budd.

8. Cited by Eppinger.

9. Förster: Ueber akute gelbe Leberatrophie, Virchows Arch. f. path. Anat. **12**:353, 1857.

10. Zenker, P.: Zur Pathologischen Anatomie der akuten gelben Leberatrophie, Deutsches Arch. f. klin. Med. **10**:166 and 167, 1872.

11. Klebs, E.: Handbuch der pathologischen Anatomie, vol. 1, p. 417; Lehrbuch der allgemeinen Pathologie, Jena, Gustav Fischer, 1889, vol. 2.

The former view prevailed, and it is now well known that cases of pure yellow atrophy, as Rokitansky has described them, are rare compared with those of pure red and mixed yellow and red atrophy.

Finally, another important feature in the picture of acute atrophy of the liver was pointed out by Marchand [12] (1895). He described a case of atrophy of the liver which had lasted for six months and which showed at necropsy, besides the picture of red atrophy, extensive regeneration in the form of adenoma-like nodules which filled the organ and projected from its surface, similar to those seen in certain forms of cirrhosis of the liver. This he termed "multiple nodular hyperplasia," a condition that is now well recognized as representing the result of long-continued attempt at repair. This also has brought to light a certain relationship between acute yellow atrophy and cirrhosis of the liver and has shown at any rate that a form of complete repair is possible, the disease not being as incurable as was previously thought.

General Features.—The three features in the anatomic picture as pointed out, namely, yellow atrophy, red atrophy and nodular hyperplasia, represent important steps in the course of the pathologic process known as acute yellow atrophy of the liver. It may be said that, schematically, yellow atrophy corresponds with the immediate effect of the injury, which amounts to a widespread necrosis of the parenchymatous elements. The next step in the process is the removal of the products of disintegration; when this is accomplished, the picture of the liver changes to red atrophy. Finally, the process of repair which probably sets in early begins to dominate the picture and when highly developed is represented by a nodular hyperplasia of the liver. However, all these three processes almost always occur side by side, resulting mostly in complex anatomic pictures and making it difficult to estimate the duration of the process. Nevertheless, such cases in which red atrophy predominates and in which there are signs that reconstruction is on the way are mostly referred to as subacute atrophy. In the majority of instances, this stage coincided with the period following the first month of the patient's illness.

PATHOLOGIC ANATOMY OF THE LIVER

Gross.—Many authors, among them Kaufmann,[13] Eppinger [14] and Herxheimer,[15] speak of an enlargement of the liver in the earliest

12. Marchand, F.: Ueber Ausgang der akuten Leberatrophie in multiple knotige Hyperplasie, Ziegler's Beitr. **17**:199 and 206, 1895.

13. Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie, ed. 7 and 8, Berlin, W. de Gruyter and Co., 1922, vol. 1, p. 712.

14. Eppinger, H.: Ueber Icterus, Klin. Wchnschr. **1**:1182, 1922.

15. Herxheimer, G.: Ueber akute gelbe Leberatrophie und verwandte Veranderungen, Ziegler's Beitr. **72**:56 and 349, 1924.

period of the disease. These statements are made on the basis of such observations as are reported by Horaczek,[16] Babes,[17] Eppinger, Senior,[18] Sternberg [19] and Hlava,[20] but a careful examination of some of these reports leaves one greatly in doubt as to whether the authors were dealing with the disease under consideration. Yet it will be seen later that an enlargement of the liver in the earliest beginning of the process as the immediate effect of the injury is, paradoxical as it may sound, pathologically compatible with a process that rapidly leads to atrophy. It is another matter that the acute atrophy may supervene on an enlarged liver from any other cause when in spite of the reduction by the atrophic process the liver will appear enlarged. Thierfelder,[6] who has studied a collection of reports of 143 cases from the literature, states that in the majority of cases in which there is only a slight degree of reduction in the size of the liver, or none at all, the explanation lies in the circumstance that the process has been developed in a liver which, by overdistention of its glandular cells with fat or by the proliferation of its interstitial tissue, has previously become enlarged. An example of such a case is to be found in a report by Liebermeister,[21] in which the liver weighed 1,520 Gm. and one by Frerichs,[22] in which the liver weighed 2,100 Gm.

Ordinarily, the liver is greatly diminished in size, even in cases of apparently short duration (from three to five days). On opening the abdomen in well marked cases, one often has to look for the liver, which is situated high up under the diaphragm, fallen back on the spinal column, and covered with coils of intestine. The diminution in size is mostly striking and in extreme cases, it is often stated, the liver may show only one fourth of its normal size. In Thierfelder's collection, in thirty-three cases occuring in patients in the prime of life, the weight of the liver ranged between 1,000 and 500 Gm. In one of White's [23] patients, a blacksmith, aged 32, with a body length of 173 cm., the liver weighed 600 Gm.

That the reduction in size is most marked in the vertical diameter was emphasized by Rokitansky and subsequently by most observers;

16. Horazcek, F.: Die gallige Dyscrasie, Wien, 1843.

17. Babes, V.: Ueber die durch Streptokokken bedingte akute Leberentartung, Virchows Arch. f. path. Anat. **136**:1, 1894.

18. Cited by Herxheimer.

19. Sternberg, C.: Zur Frage der Todesfälle nach Salvarsaninfusion, Wien. klin. Wchnschr. **26**:2096, 1913.

20. Hlava, J.: Atrophia hepatis flava acuta, Prag. med. Wchnschr. **7**:421, 1882.

21. Liebermeister, C.: Zur Pathogenese des Icterus, Deutsche med. Wchnschr. **19**:365, 1893.

22. Frerichs: Leberkrankheiten, Berlin, 1858, cited by Thierfelder.

23. White, F. W.: Acute Yellow Atrophy of the Liver, Boston M. & S. J. **158**:729, 1908.

when the liver is placed on a slab after removal from the body, it appears flattened, as if collapsed. As in all atrophic processes in the liver, the anterior border is sharp, consisting practically of nothing else but the two layers of the capsule. The latter is often cloudy and markedly lax and wrinkled as a result of the disappearance of the parenchyma. The left lobe is usually more severely affected and occasionally the subcapsular portions of the right lobe seem to have suffered least, but as a rule the process extends throughout the entire liver.

The color and consistency of the liver vary greatly. Only rarely is the process in the same stage of development throughout the liver; much more often the processes of yellow atrophy, red atrophy and regeneration are present side by side in varying extent and degree, sometimes associated with hemorrhages, making for the most complex color schemes and variation in consistency. In the earliest cases in which yellow atrophy predominates, the color, largely because of the varying intensity of the bile stain, is variously described as yellow, gamboge, saffron, ochre, or rhubarb-yellow, the consistency as soft, friable, sometimes mushy or pulpy. On the cut surface the color is particularly marked, the parenchyma bulging, the markings almost or totally obliterated. But in most cases there are alternating red and yellow parts, the latter in the form of slightly bulging, coalescent areas, from the size of a pin to that of an apple, embedded in the former which often constitute the bulk of the liver. In such cases the organ is flabby, can be folded on itself, and parts of it, especially the left lobe, can be rolled up into a scroll. Less frequently the proportion is reversed, when irregular, sunken red areas appear on a yellow background. In general, the yellow areas are bulging, soft and fragile, and the red areas are sunken, flabby and tough and are rarely leathery. The markings on cut surface are usually lost in both types of atrophy, but large lobules can sometimes be made out in the early stages of yellow atrophy and small ones in later stages of red atrophy. On smears from the cut surface, crystals of leucin and tyrosin may often be demonstrated. On exposure to the air for several hours, more often after the organ has remained on ice over night, such crystals may be seen macroscopically in the form of a cob-web-like pellicle covering certain areas of the cut surface.

In later stages (so-called subacute, subchronic or chronic cases), the bulk of the liver is red or grayish-red and of a firm consistence, often described as splenization, but scattered in its substance as gross evidence of regeneration are grayish-yellow or grayish-green, well circumscribed nodular masses which when near the surface project almost like masses of tumor. The largest ones often reach the size of a cherry or a walnut, and on section they give the appearance of tissue of the liver with

exaggerated markings, the lobules being large and irregular, their centers often distinctly green and the peripheries yellowish-gray. The number of the nodules varies with the duration of the process; they are widely scattered in the less protracted cases and are numerous, filling the liver substance, in the chronic cases when the picture is that of a coarsely nodular cirrhosis. Occasionally, the nodules have grown so far beyond the surface that they appear like polyps, sessile or pedunculated, as in case 1 of MacDonald and Milne [24] and in one of my cases. On the cut surface one can often see that the intervening red parts are traversed by irregular connective tissue trabeculae and that the blood vessels seem to have been brought close together.

The gallbladder is usually relaxed and sometimes is empty, but mostly it has been described as containing a thin or viscid, rarely lightly, more often deeply, colored bile. The large bile ducts are usually found empty, their mucosa normal, and the duodenal orifice of the ductus choledochus free from obstruction, although in the older reports statements are found that the intestinal portion of the common bile duct is swollen (Schultzen and Riess [18]) and occluded by a plug of mucus (Mann [25] and Waldeyer [26]).

Microscopic.—The primary lesion is an intense destructive process of the liver cells often spoken of as necrosis, but it differs materially from the ordinary necrosis often seen in the liver. The earliest change, as in the yellow areas, in which the lobular structure is macroscopically still recognizable, consists in a cloudy swelling and hydropic and fatty degeneration of the cells. In parts in which the process is more advanced (ochre-yellow areas), many of the cells have disappeared, leaving isolated cells with marked granular or fatty degeneration, with faintly staining nuclei, and among these irregular masses of granular cytoplasm without any nuclei. Smaller cells are also seen in the spaces between the loose collapsing capillaries; these cells are mostly stained with bile, contain fat globules and are often distinctly necrotic; also large endothelial cells, some bile-stained, others with fat droplets and phagocytized red blood corpuscles and other material, are seen. The condition, as characterized by Councilman in his observations on White's cases, is one in which the cells seem to soften and disappear by solution; they lose their outline and do not show the usual refraction and acidophil character of the ordinary necrotic liver cell.

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24. MacDonald, S., and Milne, L. S.: Subacute Liver Atrophy, J. Path. & Bacteriol. **13**:161, 1909.

25. Mann, M. D.: A Case of Infantile Parenchymatous Hepatitis, Am. J. Obst. **8**:539, 1875.

26. Waldeyer: Bacteriencolonien mit Pseudomelanose in der Leber (acute Atrophie), Wirch. Arch. **43**:533, 1868.

The destructive process is so rapid that even in the earliest cases many areas are found (red atrophy) from which the liver cells have completely disappeared, leaving a shrunken lobule with much granular detritus and dilated sinusoids filled with blood. Among the masses of detritus that occupy the place of the cells, crystalline and granular bile pigment, fat globules, blood pigment, and phagocytic endothelial cells (Kupffer cells) may be seen, the latter often loaded with pigment and fat. Frequently many red blood corpuscles are found among the detritus, and this contributes to the red color of the tissue, largely due to the marked filling of the sinusoids.

As the process advances, round cell infiltration usually appears in the portal spaces, and numerous small bile ducts become prominent. Also, remaining liver cells may begin to show early evidence of proliferation, and in places in which the débris has been removed, increase of connective tissue proceeding from the portal spaces into the lobule is noticed. Thus, processes of regeneration appear early, forming an important feature of the histologic picture of acute atrophy of the liver at almost any stage; but there is some difference of opinion about its mechanism.

Regeneration.—Attempts at reconstruction are rarely missed microscopically, except in cases that are rapidly fatal, and in older so-called subacute cases newly formed tissue of the liver can almost always be observed macroscopically, as stated in the foregoing, in the form of grayish-yellow or greenish-yellow nodules. The nodules generally resemble tissue from the liver, consisting of characteristic cells that are apparently newly formed. Most of these are larger than the normal liver cells and are often binucleated and multinucleated; their cytoplasm is clear and swollen. The others are smaller and have a granular cytoplasm. They are arranged in irregular lobular masses in the form of wide trabeculae (several cells abreast) in which bile capillaries, usually strongly injected with bile, are to be seen; their blood capillaries are narrow, appearing compressed; but rarely do they show any typical lobular arrangement, their central veins often being found at the periphery. Occasionally they show necrosis in their central parts, possibly as an expression of a continuation or recurrence of the destructive process.

The origin of the new liver parenchyma was attributed by some of the earlier authors (Waldeyer and Zenker) to the proliferated bile ducts which have been seen to appear in the portal spaces even in early stages of the process, and which by progressive differentiation are supposedly transformed into liver cells; other authors (Klebs and Perls [27]) were opposed to this view. Later, the process of regeneration was studied in protracted cases including multiple nodular hyper-

27. Perls: Allgemeine Pathologie, 1877, p. 171.

plasia by Meder,[28] Marchand,[12] Stroebe,[29] Barbacci,[30] McCallum [31] and others. All these authors, like Klebs, found definite evidence of the origin of new liver cells from old ones which had survived the degenerative process. But with the exception of Barbacci, they all admitted also the production of liver cells to a considerable extent from the proliferated bile ducts. Experimental work on liver regeneration at that time by Ponfick [32] and by Podwyssozki,[33] especially the latter, seemed to favor this theory of a dual origin.

However, Ribbert [34] and Carraro,[35] in subsequent studies of regeneration following experimental necrosis in animals, failed to prove the origin of liver cells from bile ducts. Ribbert also considers the origin of liver cells from bile ducts improbable on ontogenetic grounds, pointing out that in the first anlage of the liver, differentiation of bile ducts and liver cells take place independently. Another view is that of some English authors, notably Macdonald and Milne,[24] who deny altogether the occurrence of proliferation of the bile duct in these livers; they claim that the preexisting bile ducts have merely become more prominent as a result of the absence of liver cells. This is denied by Miller and Rutherford,[36] who emphasize the multiplication of the ducts, resulting in the production of ramifying canaliculi to be linked up with the new liver cells which latter, however, are produced exclusively by preexisting ones.

With this presentation of the subject of regeneration of liver tissue, the surface had merely been touched. The subject is complicated, and it would lead too far if one were to enter into all the studies that were made on the subject based on experimental as well as human material. Suffice it to say that at the present, no one denies the important rôle the surviving liver cells play in the regeneration in acute yellow atrophy.

28. Meder, E.: Ueber akute Leberatrophie mit besonderer Berücksichtigung der Regeneration, Ziegler's Beitr. **17**:143, 1895.

29. Stroebe, H.: Zur Kenntnis der akuten Leberatrophie mit besonderer Berücksichtigung der Spätstadien, Ziegler's Beitr. **21**:379, 1897.

30. Barbacci, O.: Ueber Ausgang der akuten Leberatrophie in multiple knotige Hyperplasie, Ziegler's Beitr. **30**:49, 1901.

31. McCallum, W. G.: Regenerative Changes in the Liver After Acute Yellow Atrophy, John Hopkins Hosp. Rep. **10**:375, 1902.

32. Ponfick, E.: Experimentelle Beiträge zur Pathologie der Leber, Wirch. Arch. **118**:209, 1889; **138**: (supp.) 81, 1895.

33. Podwyssozki, W.: Experimentelle Untersuchungen ueber die Regeneration des Drüsengewebes, Part I, Untersuchungen ueber die Regeneration des Lebergewebes, Ziegler's Beitr. **1**:259, 1886.

34. Ribbert, H.: Zur Regeneration der Leber und Niere, Arch. f. Entwicklungsmechanik **18**:67, 1904.

35. Carraro, A.: Ueber Regeneration der Leber, Virchows Arch. f. path. Anat. **195**:462, 1909.

36. Miller, J., and Rutherford, A.: Liver Atrophy, Quart. J. Med. **17**:81, 1923-1924.

The frequent observation of mitotic or amitotic figures in these cells, which are also often the seat of a true compensatory hypertrophy, leaves little doubt as to the ability of these cells to regenerate. Moreover, according to the majority of authors, this mode of regeneration is the most important one for the reconstruction of the liver. The controversy is chiefly about the bile ducts. These are usually found in great number in the periphery of the depleted lobule of the red parts of the liver, in the form of bands of cells similar to those so frequently found in cirrhosis. Larger structures resembling these, "tubules" or "pseudotubules" as they are often called, can be seen farther in the shrunken lobule sometimes almost reaching the central vein. Less frequently, they can also be found near new tissue in the liver. These have been interpreted by many authors, including Meder, Stroebe, McCallum and Ibrahim,[37] as sprouts from the smaller bile ducts of the portal spaces on their way to produce new liver cells by differentiation and proliferation of their elements. It was even claimed by Dinkler [38] that he had successfully injected these tubules through the bile duct. Marchand, too, considered them as sprouts from the interlobular bile ducts, but in part only, the other part being formed by remnants of the old liver cells. Both the interlobular bile ducts and the residual cells of the liver participate in their formation, according to Marchand; while the former grows from the periphery into the loose mesh-work of the lobule, the latter constantly supply them with new "building material." An essentially similar view is held by Muir.[39] According to other authors, among them Klebs, Ribbert, Barbacci, Herxheimer and Gerlach,[40] these tubules represent old, surviving trabeculae of liver cells and have no connection whatever with the interlobular bile ducts; lately, Herxheimer claimed to have brought sufficient proof of the truth of this view. By means of Eppinger's method of staining for bile capillaries, he succeeded in demonstrating such capillaries in the tubules in question. These capillaries take an axial course and show lateral bulgings and varicosities, thus corresponding closely with the normal trabecular capillaries and their lateral intercellular branches. Similar results were obtained in two cases of

37. Ibrahim, A. Bey: Zur Kenntnis der akuten gelben Leberatrophie insbesondere der dabei beobachteten Regenerationsvorgänge, Munchen. med. Wchnschr. **48**:780 and 838, 1901.

38. Dinkler: Ueber Bindegewebs-und Gallengangsneubildung in der Leber bei chronischer Phosphorvergiftung und sogenannter akuter gelber Leberatrophie, Inaug. Diss., Halle, 1887, cited by Herxheimer.

39. Muir, R.: On Proliferation of the Cells of the Liver, J. Path. & Bacteriol. **12**:287, 1908.

40. Herxheimer, G., and Gerlach, W.: Ueber Leberatrophie und ihr Verhältnis zu Syphilis und Salvarsan, etc., Ziegler's Beitr. **68**:93, 1921.

acute yellow atrophy by Blum.[41] According to these two authors, then, the "pseudotubuli" are nothing more than persisting (not newly formed), somewhat altered trabeculae of liver cells with dilated lumen, and at any rate liver parenchyma in acute atrophy is regenerated exclusively from liver cells.

There has also been a considerable controversy about the zonal form of the necrotic process. The earlier authors (Zenker,[10] Hirschberg[42] and von Khalden[43]) and the Vienna school of pathologists, among whom may be mentioned Paltauf,[44] Kretz[45] and Sternberg,[19] described the process as beginning in the center of the liver-lobule. Among later authors who hold this view may be mentioned Ceelen,[46] Wells and Bassoe,[47] and lately also McCallum.[48] In one of White's cases (case 3), Councilman describes a disappearance of liver tissue, chiefly in the center, yet Thierfelder, Kimura,[49] Hess,[50] Eppinger and many others maintain that the process begins at the periphery of the lobule. The destructive process is usually so rapid that not many cases are well adapted for the study of this subject. Even in such cases one finds a difference of opinion. Thus, in the case of Lanz,[51] which is supposed to have lasted only four days, the author describes the necrosis as peripheral, while in Ceelen's case of eight days' duration it was central. Other opinions are: that the necrosis begins in the intermediate zone (Wegerle[52]); that it varies (Herxheimer) and that no part of the lobule is more affected than another (Miller and Rutherford). The question is of some importance, and I shall return to it later.

41. Blum, R.: Zur Frage der Leberregeneration insbesondere der sogenannten schlauchartigen Bildungen bei Leberatrophie, Ziegler's Beitr. **72**:95, 1924.

42. Hirschberg: Drei Falle von akuter gelber Leberatrophie, Inaug. Diss., Dorpat, 1886, cited by Herxheimer.

43. Von Khalden: Ueber akute gelbe Leberatrophie und Lebercirrhose, München. med. Wchnschr. **44**:1096, 1897.

44. Paltauf, R.: Ueber Veränderungen der Leber bei Phosphorvergiftung, Verhandl. d. deutsch. path. Gesellsch. **5**:91, 1903.

45. Kretz, R.: Pathologie der Leber, Ergebnisse der allgemeinen Pathologie, Lubarsch Ostertag **8**:473, 1902.

46. Ceelen, W.: Eklampsie combiniert mit akuter gelber Leberatrophie, Charité-Ann. **35**:405, 1911.

47. Wells, H. G., and Bassoe, P.: Acute Yellow Atrophy of the Liver, J. A. M. A. **44**:685 (March 4) 1905.

48. McCallum, W. G.: Text Book of Pathology, ed. 3, Philadelphia, W. B. Saunders Co., 1924, p. 313.

49. Kimura: Ein weiterer Fall von subakuter gelber Leberatrophie mit vorgeschrittener Regeneration, mit besonderer Berücksichtigung des Glycogengehaltes, Ziegler's Beitr. **58**:211, 1914.

50. Hess, O.: Ueber die bei der akuten gelben Leberatrophie auftretenden Regenerationsprozesse, Ziegler's Beitr. **56**:22, 1913.

51. Lanz, F.: Ueber die Behandlung der Phosphorvergiftung, Berl. klin. Wchnschr. **32**:878, 1895.

52. Wegerle, O.: Subakute Leberatrophie mit knotiger Hyperplasie auf tuberkulöser Grundlage, Frankfurt. Ztschr. f. Path. **15**:89, 1914.

Chemical Analysis of the Liver.—The presence of leucin and tyrosin has already been mentioned. It was first detected by Frerichs microscopically. The outstanding analyses of the liver in acute yellow atrophy are those of Taylor [53] and of Wells,[54] in whose "Chemical Pathology" the subject is adequately presented. The liver has been found to have a high water and a low fat content, its yellow color being chiefly due to bilirubin. It contains little if any glycogen, and lecithin is decreased. There is a striking increase in the organic nonlipoidal phosphorus. Most important, however, is the abundance in the liver of many of the free amino-acids demonstrable in protein digestion; purine bodies, among which uric acid has been demonstrated in crystalline form by M. B. Schmidt [55] and hemolytic substances in the form of free fatty acids (Joannovicz and Pick [56]) also are present.

ANATOMIC CHANGES IN OTHER ORGANS

A good general picture of the postmortem changes of the entire body has been given in the foregoing in the words of Rokitansky. These have been studied in considerable detail, and more have been described.

Spleen.—In Thierfelder's series, two thirds of the cases showed acute swelling, the organ often being enlarged to twice the normal size. Salffner [57] found the spleen enlarged in forty-two out of fifty-five cases. Eppinger, who states that he has never failed to find enlargement of the spleen in acute atrophy, characterizes the enlargement as a chronic splenic tumor; histologically, he has found free blood in the pulp and hemosiderin. According to Herxheimer, slight swelling of the spleen is found in most cases. Both Eppinger and Herxheimer regard the enlargement mainly as the effect of the same injurious substance that produces the changes in the liver, although portal stasis may also be a factor, especially in protracted cases.

Bone Marrow.—Eppinger has also noticed hyperplasia (red) of the bone marrow in all his cases, as has Herxheimer; the former considers this in connection with his observations in the spleen as pointing to excessive destruction of blood.

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53. Taylor, A. E.: A Chemical Study of the Liver from a Case of Acute Yellow Atrophy of the Liver, J. M. Research **3**:424, 1902.

54. Wells, H. G.: Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Co., 1925, p. 613; The Chemistry of the Liver in Acute Yellow Atrophy, J. Exper. Med. **9**:627, 1907.

55. Schmidt, M. B.: Die Stoffwechselvorgänge bei akuter gelber Leberatrophie, Ziegler's Beitr. **69**:222, 1921.

56. Joannovicz, G., and Pick, E. P.: Ueber hamolytisch freie Fettsaure in der Leber bei akuter gelber Leberatrophie und Phosphorvergiftung, Berl. klin. Wchnschr. **47**:928, 1910.

57. Salffner, O.: Zwei Falle von akuter gelber Leberatrophie, Inaug. Diss., Munich, 1889.

Pancreas.—Not infrequently, small foci of fat necrosis (inflammatory) have been found associated with acute atrophy (Emmerich,[58] Eppinger, Seyfarth [59] and Umber [60]), and Salomon [61] has reported a case showing extensive fat necrosis. This, too, is generally considered as concomitant with the changes in the liver as frequently observed in cirrhosis of the liver.

Ascites.—According to Riess,[62] the presence of moderate amounts of ascitic fluid that is usually bile-stained is much more common than was previously assumed. Herxheimer asserts, in agreement with many observers and in opposition to Milne [63] and Umber, that after the sixth week the presence of ascites is almost the rule, although it is exceedingly rare before that period.

Heart and Kidneys.—Fatty degeneration seems to be a constant though comparatively later feature in the heart and kidneys, especially in the latter. Forty-one of the sixty-six cases of Salffeld showed degeneration of the kidneys and thirty-nine, degeneration of the heart. Meyer,[64] who found fat in the capsule of the glomerulus and in the convoluted tubules, considers it the result of a lipemia—as a nephrosis. He also demonstrated considerable increase of fat chemically. Necrosis of the kidney tubules has been found by Janssen,[65] Wells and Bassoe,[47] Verse [66] and Herxheimer; Schmidt also saw calcification of the tubules.

Other Observations.—Fatty degeneration of the skeletal muscles was found by Paulicki and Wagner; Zenker's degeneration, by Schmidt; fatty degeneration of the glandular cells of the stomach and those of the intestinal villi, by Bollinger,[67] Hlava [20] and Rosenheim; [68] retinal

58. Emmerich: Akute Gelbe Leberatrophie, München. med. Wchnschr. **68**: 999, 1921.

59. Seyfarth, C.: Leberatrophein, Centralbl. f. allg. Path. u. path. Anat. **31**:255, 1921.

60. Umber, F.: Leberatrophie, Berl. klin. Wchnschr. **57**:125, 1920.

61. Salomon, G.: Zur Etiologie der akuten gelben Leberatrophie, Berl. klin. Wchnschr. **54**:112, 1917.

62. Riess, L.: Phosphorvergiftung und Leberatrophie, Berl. klin. Wchnschr. **44**:54 (Festnummer), 1905.

63. Milne, L. S.: The Histology of Liver Cell Regeneration, J. Path. & Bacteriol. **13**:127, 1919.

64. Meyer, E.: Das Verhalten der Niere bei akuter gelber Leberatrophie, Virchows Arch. f. path. Anat. **236**:279, 1922.

65. Janssen: Akute gelbe Leberatrophie bei florider Syphilis, Inaug. Diss., Berlin, 1911, cited by Herxheimer.

66. Verse: Zur akuten Leberatrophie, Berl. klin. Wchnschr. **57**:127, 1920.

67. Bollinger, O.: Leberatrophie und Phosphorvergiftung, Deutsches Arch. f. klin. Med. **5**:149, 1869.

68. Rosenheim, T.: Akute gelbe Leberatrophie bei einem Kinde, Ztschr. f. klin. Med. **15**:441, 1889.

hemorrhages with fatty degeneration and incrustation with tyrosin crystals, by Litten;[69] atrophy of the thyroid in four out of seven cases by Eppinger.

Urine.—The quantity usually diminishes toward the end; the specific gravity becomes correspondingly increased and the sediment heavy. Albumin is mostly present in traces, and occasionally a few casts are found. Sugar is absent. Bilirubin is almost always present, but it tends to diminish in quantity toward the end. Eppinger considers this terminal diminution in bilirubin characteristic for acute yellow atrophy and the same, he thinks, probably applies to biliary acids. The total nitrogen is increased, and the urea diminished. Ammonia may be increased, probably not so much the result of deficient formation of urea as of an increased formation of organic acids. These are found in the form of sarcolactic, oxymandelic, aceto-acetic, and beta-oxybutyric acids. There is also an increase in etheral sulphates. Uric acid is increased, and in patients who have ultimately recovered, enormous quantities of it have been found (Quincke[70]).

Leucin and tyrosin crystals have been found in the urine in the early days, and their discoverer (Frerichs) claimed that they were present in all cases. The tyrosin excreted in some cases amounted to 1.5 Gm. a day. This, however, has not been the subsequent experience, and there are many cases in which these substances could not be demonstrated. In Thierfelder's collection, they were not found in seven out of thirty-four cases. In the unconcentrated urine, leucin is less likely to be found than tyrosin. By careful chemical methods, Schum (quoted by Wells) could demonstrate only leucin and tyrosin in two out of seven cases. Geronne[71] states that only exceptionally were leucin and tyrosin found in typhoid fever, smallpox, pernicious anemia, leukemia and severe diabetes, and that Abderhalden found them in a case of obstructive jaundice due to the presence of a stone in the common bile duct. He points out that, according to Minkowski, the appearance of these substances in the urine is dependent on the rate of disintegration of the liver parenchyma; when the process is slow, their excretion in the urine may be missed. Geronne found leucin and tyrosin in forty-six cases of jaundice of various grade, the etiology of which was as follows: In two out of three cases of acute yellow atrophy; in three out of six cases of grave jaundice in the secondary stage of syphilis; in eight out of thirty cases of so-called catarrhal jaundice, and in two out of seven cases of cholelithiasis. Finally,

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69. Litten, M.: Augenveränderungen bei akuter Leberatrophie, Ztschr. f. klin. Med. **5**:58, 1882.

70. Quincke, H.: Diseases of the Liver, in Nothnagel's System **18**:630, 1899.

71. Geronne, A.: Zur Pathogenese einiger Formen des Icterus, Klin. Wchnschr. **1**:828, 1922.

Geronne warns against the confounding of crystals of ammonium urate with those of leucin; the latter have no prickles, a lighter contour and no refractility. He also warns against mistaking bilirubin for tyrosin needles, the former being intensely brown-red.

Blood.—The bilirubin may be markedly increased.[72] Here too leucin and tyrosin have been demonstrated (Neuberg and Richter[73]) as well as lysin (Jacoby[74]). There is a high amino-nitrogen content, and the urea-nitrogen may fall below 50 mg. per hundred cubic centimeters. Sugar is at first increased; later, it is diminished and sugar tolerance is reduced. Lysins and cholesterol are increased as well as lipase, and there is a loss of fibrinogen and globulin. The coagulability of the blood is delayed, and the bleeding time increased.

Cytologic Changes.—Occasionally, the number of erythrocytes is increased, and the blood shows a corresponding rise in hemoglobin, as reported by Pribram and Walter[75] and by Umber. According to Eppinger, they are frequently diminished (2,500,000). Occasionally also, the leukocytes are increased (15,000), but they may fall to 2,000 when there is an associated relative lymphocytosis (Eppinger). On the other hand, Weigeldt[76] always found lymphopenia and moderate polynucleosis. The same author claims to have seen vacuoles filled with cholesterin esters in many neutrophil leukocytes. In spite of the increased bleeding time, the platelets are not diminished, and in spite of the presence of hemolytic substances, the resistance of the erythrocytes is not reduced (Eppinger).

Feces.—There is considerable variation in the feces. Most often they are described as clay-colored, but they are not altogether free from bile pigment, especially on chemical examination. As a result of hemorrhages in the intestinal mucosa, they are frequently mixed with decomposed blood. The presence of neutral fat was demonstrated in two out of six cases by Eppinger. He was also able to examine the duodenal contents in one case one day before the outbreak of the graver symptoms. These showed much bile but not any biliary acids. The latter were also absent in the bile from the gallbladder in two cases, as shown by direct postmortem examination.

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72. Reports as to the quantity are not available. In one case in our hospital in which the diagnosis was made clinically and necropsy could not be obtained, the van den Bergh reaction was immediately direct and the quantity, 49 units.

73. Neuberg, C., and Richter, P. F.: Ueber das Vorkommen von freien Aminosäuren (Leucin, Tyrosin, and Lysin) im Blute bei akuter gelber Leberatrophie, Deutsche med. Wchnschr. **30**:499, 1904.

74. Jacoby, H.: Ueber Hepatolyse (akute gelbe Leberatrophie) bei Lues, Klin. Wchnschr. **3**:840, 1924.

75. Pribram, H., and Walter, J.: Zwei Fälle von akuter gelber Leberatrophie, Prag. med. Wchnschr. **37**:220, 1912.

76. Weigeldt, W.: Akute gelbe Leberatrophie, Arch. f. klin. Med. **135**:358, 1921; Deutsche med. Wchnschr. **47**:1221, 1921.

NATURE OF THE PATHOLOGIC PROCESS AND PATHOGENESIS

From the description of the histologic changes given in the foregoing, it will be seen that the earliest lesion found in the liver is represented by a destructive process in the cells of the liver. Generally speaking, this may be and often is termed necrosis, but the picture does not entirely conform to that of ordinary necrosis, either in the liver or anywhere else. One sometimes gains the impression that both the disintegration and the removal of the debris is so rapid that the cells have not had time to develop the characteristic appearance of necrosis with which one is ordinarily familiar. It seems useless to enter into the old controversy as to whether this initial process is an inflammatory one, as insisted on by Buhl and Förster, or a degenerative one, as maintained by Rokitansky and Zenker and Klebs, as it is now meaningless. Light was gained on the question from the experimental work of Salkowski [77] and of Jacoby,[78] through whose researches physicians became acquainted with the process of autodigestion, or autolysis, as Jacoby called it, a process that manifestly depends on the action of enzymes. On removal of a piece of liver from the body under sterile conditions, it will after a while be found to have digested itself, with the result that many of the products of protein digestion (albumoses, peptones, leucin and tyrosin, etc.) will be demonstrable in the remaining material. On the other hand, as stated in the foregoing, the chemical analysis of the liver in acute atrophy yielded similar products (Taylor, Wells and Neuberg). Jacoby further showed that this autolysis in the liver in vitro proceeds much more rapidly in the liver of an animal that had been previously poisoned with phosphorus. The similarity of the two processes then and the relation that exists between acute yellow atrophy and phosphorus poisoning, as will be seen later, gradually led to the recognition that the injury in the liver which brings about its rapid shrinkage is a digestive process—an autolysis. Paltauf early recognized this for phosphorus poisoning, and Albrecht [79] and later Liefmann [80] came to the same conclusion concerning acute atrophy on the basis of their histologic studies of autolyzed tissue.

Before going any further, I must touch on the question lately raised by Umber.[81] He had the opportunity to examine a liver showing acute

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77. Salkowski, E.: Autodigestion der Organe, Berl. klin. Wchnschr. **16**:90, 1890.

78. Jacoby, M.: Ueber die Beziehungen der Leber und Blutveränderungen bei Phosphorvergiftung zur Autolyse, Ztschr. f. physiol. Chem. **30**:174, 1900.

79. Albrecht, E.: Ueber trübe Schwellung und Fettdegeneration, Verhandl. d. deutsch. path. Gesellsch. **4**:63, 1904.

80. Liefmann, E.: Zur Kenntnis der Frühstadien der akuten gelben Leberatrophie, Centralbl. f. allg. Path. **16**:465, 1905.

81. Umber, F.: Leberatrophie, Deutsche med. Wchnschr. **45**:537, 1919.

yellow atrophy during life at an abdominal operation, and he found that, although the excised piece showed typical histologic changes, the gross appearance of the liver did not possess the characteristics usually seen in the organ at postmortem; the liver was more of a bluish-red color and did not show any yellow parts at all. The patient recovered, so that Umber was unable to compare his observations with the postmortem appearance of the same organ. Nevertheless, his observation led him to conclude that the liver of acute yellow atrophy as seen at necropsy is a product of postmortem digestion. This is not a new idea, as the possibility had already occurred to Budd in 1846. Umber's observation is undoubtedly correct, but the type of liver he has seen during life differs little in appearance at postmortem, as Fraenkel [82] has shown and as I have lately had occasion to observe. Cases in which operation is performed are usually protracted ones, showing mostly red atrophy and regeneration and none of the yellow color of the earlier stages. The color of the liver at necropsy is always somewhat lighter than it is during life, on account of its loss of blood. On the other hand, there are enough cases on record in which the necropsies have been performed shortly after death, and the appearance of the liver was typical.[83]

Above all, Fraenkel [84] and Hanser [85] had the opportunity to compare the two conditions, and they could not find any essential difference between the histologic picture of the tissue of the liver gained at operation and at necropsy.

Regarding the agency that brings about the autolysis in the liver, acute yellow atrophy or conditions simulating it closely had been observed for a long time in cases of human poisoning with such substances as phosphorus, chloroform, mushrooms, etc. It could therefore be assumed on the basis of what amounted to human experiments that in idiopathic atrophy of the liver the injury of the liver cells leading to their autolysis is due to some form of poison, either bacterial or metabolic. It goes without saying that the poison, while injuring the cell, must not at the same time destroy the autolytic enzymes. The hypothesis is stated by Wells and Bassoe as follows: "It seems possible that any poison which does not directly cause death but which causes a severe injury to the liver cells without at the same time destroying the autolytic

82. Fraenkel, E.: Bemerkungen ueber akute gelbe Leberatrophie, Deutsche med. Wchnschr. **46**:225, 1920.

83. In one of my cases showing an acute form of the disease, in which the circumstances were such that the autopsy had to be performed in less than thirty minutes after the patient had ceased breathing, the appearance of the liver was characteristic.

84. Fraenkel (footnote 82).

85. Hanser, R.: Zur Frage der Akuten Gelben Leberatrophie, Virchows Arch. f. path. Anat. **233**:150, 1921.

enzymes, so that the cells die and undergo rapid autolysis, may produce a condition identical with or similar to acute yellow atrophy." Eppinger also considers another factor, namely, a disturbance in the regenerative power of the liver. As is well known, this is ordinarily remarkably efficient, but the atrophic liver may not have possessed this power sufficiently to begin with, or has lost it completely or only to some extent, as the result of the action of the same poison that injured the cell. Eppinger was led to this idea by his observation of an atrophy of the thyroid gland in four of his cases. He then studied the influence of thyroidectomy on regeneration after partial extirpation of the liver in rabbits and found that, unlike normal animals, such rabbits survive the operation only from twenty-four to forty-eight hours, not showing any regeneration of the liver. Yet on the one hand, the exquisite regenerations one observes in acute yellow atrophy, even during the time the injurious process is still active and especially after it has ceased, would seem to speak against such a hypothesis; on the other hand, if the thyroid secretion were really of importance for regeneration of the liver, a case like the one reported by Kerr and Rusk,[86] in which there was an enormous hyperplasia of the thyroid (and a basal metabolic rate of 78.8), would point strongly against a weakened regenerative power in the liver. Eppinger also believes that both the spleen and the pancreas are affected by the same injurious substance simultaneously with the liver. This may or may not be so.

However, the hypothesis of Quincke that the digestion of the cells of the liver may be brought on by a backing up of pancreatic secretion into the liver in consequence of an obstruction to its outflow at the duodenal opening can hardly be accepted. Obstructions at the duodenal orifice are not the rule in acute yellow atrophy, and according to Opie,[87] because of greater pressure in the bile ducts, such obstructions lead rather to a flow of bile into the pancreas than in the reverse direction. Moreover, Best [88] was unable to produce typical changes in the liver by the injection of trypsin into the bile duct in a variety of animals.

It is only with such a process as autolysis, whereby the channels for efficient absorption of the liquified tissue remain more or less intact, that the most conspicuous feature of the condition, namely, the rapid shrinkage of the liver, can best be harmonized. The autolysis of the liver is probably also responsible for a great part of the amino-acids in the blood and urine, the other part being due to hepatic insufficiency. It is

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86. Kerr, W. J., and Rusk, G. Y.: Acute Yellow Atrophy Associated with Hyperthyroidism, M. Clin. N. Amer. **6**:445, 1922.

87. Opie, E. L.: Diseases of the Pancreas, Philadelphia, J. B. Lippincott Co., 1903.

88. Best: Acute Yellow Atrophy of the Liver, Thesis, Chicago, 1903, cited by White, Wells and Herxheimer.

now generally assumed that they represent products of digestion of the liver itself as well as those of peptic digestion which the liver has failed to deaminize (Wells).

Most of the other phenomena, however, are generally ascribed to hepatic insufficiency. Thus, the tendency to hemorrhages is usually regarded, in part at least, as due to the decreased coagulability of the blood consequent on deficient formation of fibrinogen and fibrin ferment. However, some additional factor which has a damaging effect on the blood vessels must be involved in the process, as decreased coagulation of the blood alone, as, for instance, in hemophilia, does not lead to extravasation of blood. The severe toxemia, as is manifested particularly by the cerebral symptoms, is sufficiently accounted for by the failure of the intermediary metabolism, with the resulting accumulation of poisonous products, combined perhaps with imperfect oxygenation following the impairment of the oxidizing function of the liver. It seems unnecessary to assume, as the older authors did, that the organs are generally affected by the same poison that attacks the liver. The anatomic characteristics in the other organs of the body hardly warrant such an assumption. On the contrary, it seems that the liver in acute yellow atrophy bears the brunt of the condition; this is unlike the conditions allied with acute yellow atrophy, particularly phosphorus poisoning, for as Wells points out, the great change in the liver would not be possible if the poisons affected the heart, kidney or brain as they do the liver; in other words, the patient would die before the changes in the liver had time to develop.

Nature of the Jaundice.—In modern classifications of jaundice, the jaundice of acute yellow atrophy is usually placed in the group called toxic and infective (McNee,[89] Rolleston[90] and others). This group embraces a large number of conditions in which there is neither a gross obstruction to the outflow of bile nor a marked excess of hemolysis (catarrhal jaundice, many forms of icterus gravis and the jaundice of infectious diseases, such as pneumonia and syphilis). On the mechanism of this type of jaundice, there is no unanimity of opinion. Most of the French investigators, particularly Lemierre[91] and Brulé,[92] explain the jaundice in this group of diseases on the basis of a disordered function of the liver cells. Quite in accord with the results of the latest

89. McNee, J. W.: Discussion of Degenerative Diseases of the Liver, Brit. M. J. **2**:1055, 1922.

90. Rolleston, H. D.: Diseases of the Liver, Oxford Medicine **3**:315, 1921.

91. Lemierre, A.; Brulé, M., and Garban, H.: Les retensions biliaires par lesion de la cellule hepatique, Semaine med. **34**:130,1914.

92. Brulé, M.: Recherches recentes sur les ictères, 1919; Recherches sur l'ictère, These Paris, ed. 3, 1922, p. 192.

experiments on the formation of bile pigment (Whipple,[93] McNee,[94] Rich[95] and Mann[96]), Brulé believes that bilirubin arrives completely formed in the hepatic cell; that the rôle of the latter is not secretory but excretory, and that by virtue of a glandular function it regulates the elimination of bile much like the renal cells regulate the elimination of urea and chlorides. Ordinarily, as the pigment reaches the cell, it is passed on to the bile capillary, but in the case of a disturbance in the function of the cell it does not reach the capillary and is therefore retained in the blood. According to Brulé, all functional disturbances of the cell of whatever nature may be followed by biliary retention. Certainly if one accepts the modern doctrine of extrahepatic formation of bile in the human organism there ought not to be any difficulty in explaining the jaundice of acute yellow atrophy. The circumstances would be analogous to the retention of urea in cases of extensive destruction of the kidneys. This simple explanation of the jaundice of acute yellow atrophy was suggested by Liebemeister in 1895.

However, as much as others are reconciled to some form of extrahepatic formation of bile, they still believe or did believe in the period in which they wrote about it that the liver is nevertheless of primary importance for the manufacture of bile pigment—if not by the parenchymatous elements, at least by the Kupffer cells. Thus, Eppinger refers to three different modes of bile retention for an explanation of the mechanism of the jaundice in acute yellow atrophy; first, to actual intrahepatic obstruction on the ground of the presence of those capillary bile thrombi which he had demonstrated in other conditions. This coincides with the old theory of Stadelmann,[97] according to which all jaundice was either grossly obstructive or was due to intrahepatic obstruction. The second mode of bile retention was due to a condition which Eppinger named "jaundice by destruction of hepatic parenchyma," which means a laceration of the liver cells through which secretion is presumably poured into the circulation. Eppinger was able to demonstrate such lacerations in a certain part of the liver at an early stage of acute yellow atrophy. Since the Kupffer cells usually survive the autolytic process in acute yellow atrophy, he also considers the third mode of retention as due to the possibility of these cells throwing the

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93. Whipple, G. H., and Hooper, C. W.: Hematogenous and Obstructive Icterus, J. Exper. Med. **17**:593 and 612, 1913.

94. McNee, J. W.: Experiments on Haemolytic Icterus, J. Path. & Bacteriol. **18**:325, 1913-1914.

95. Rich, A. R.: Formation of Bile Pigment, Physiol. Rev. **5**:182, 1925.

96. Mann, F. C.: Site of Formation and Source of Bilirubin, Arch. Path. **2**:516 (Oct.) 1926.

97. Stadelmann, E.: Icterus bei Toluylendiamin-, Arsen-, und Phosphorvergiftung, Arch. f. exper. Path. **14**:231, 1882; **15**:236, 1883.

pigment they manufacture directly into the circulation because of the absence of the liver cells or their inability to receive it. Herxheimer agrees fully with Eppinger on the first two mechanisms, but is uncertain about the third.

Yet, in the dehepatized dogs of Mann and his collaborators, the urine and blood become pigmented soon after the operation, and at autopsy appreciable jaundice is present. In earlier stages of acute yellow atrophy, it seems that at least a great part of the jaundice must be due to loss of liver substance. It does not require any great stretch of the imagination to assume that even the remaining liver cells are unable to perform their excretory function, but even if they were able to do so, there would not be enough left to eliminate bile in sufficient quantity to prevent jaundice. Doubtless the Kupffer cells, which probably produce bile pigment, also contribute their share of bile to the blood. In later stages, the mechanism probably becomes more complicated. The bile thrombi of Eppinger can readily be found in the regenerated areas by any one who looks for them, and the question as to whether these are responsible for the jaundice or the disordered function of regenerated cells in the sense of Brulé, or both, is difficult to decide.

ETIOLOGY

Age.—It is well known that young people are much more frequently attacked by acute yellow atrophy than old ones; it is most common between the ages of 20 and 30. In a total of 143 patients in Thierfelder's collection of reports, seventy were between 20 and 29. Quincke states that about one half of the cases occur between 20 and 30. Herxheimer's collection of 200 reports of cases shows 140 patients to be under 30 and only twenty older than 40. Many cases have also occurred in children, and several cases have been reported in new-born infants (Aufrecht,[98] Babes[17] and Hecker[99]). Of all the reports published, Herxheimer calculates that 10 per cent occurred in children not older than 13 years.

Sex.—It is equally well known that women are affected much more often than men. Thierfelder's series shows a proportion of 8 to 5. Undoubtedly, the predisposing influence of pregnancy contributes to the high percentage of cases in women; still, viewed from the obstetrical side, the incidence of acute yellow atrophy in pregnancy seems to be remarkably low, judging from the figures of Braun[100] in 1887 (1:2,800) or those of Späth[101] in 1854 (2:2,300).

98. Aufrecht: Akute Leberatrophie bei Sclerema neonatorum, Centralbl. f. inn. Med. **17**:273, 1896.

99. Hecker: Akute Leberatrophie nach Pilzvergiftung, Monatschr. f. Geburtsh. **21**:210, 1867.

100. Braun: Inaug. Diss., cited by Thierfelder.

101. Cited by Thierfelder.

Alcohol.—Alcohol does not seem to be as prominent a predisposing factor as the older authors thought. Quincke is not satisfied that it is a factor, but Rolleston states that in a few instances alcoholic excess has been followed by acute atrophy. Herxheimer, quoting Oppolzer, Leudet and Wolf, states that single large doses of alcohol have led to acute atrophy.

Pregnancy.—That pregnancy is a predisposing factor is certain. More than half of the cases are said to have occurred in pregnancy. However, the figures in the earlier statistics are probably too high, as many of the cases included might have been phosphorus or chloroform poisoning. Herxheimer considers Salffner's figures of twenty out of seventy cases unusually high, and points to the paucity of reports of such cases in several other smaller collections. The disease occurs mostly in the second half of pregnancy, although many cases have occurred in the puerperium, and a few in the earliest period of pregnancy (Beatty [102]). Since it is generally recognized that previous damage to the liver, such as repeated attacks of jaundice and fatty liver due to alcohol or cirrhosis, predisposes to acute yellow atrophy, the great frequency with which it is associated with pregnancy may be explained on similar grounds. Hofbauer [103] has described anatomic changes in the liver in pregnancy in the form of central fatty degeneration, a loss of glycogen in the cells and certain vascular disturbances. Necrosis of the liver, which may resemble the necrosis of well known poisons or acute atrophy, may occur with the toxemia of pregnancy, especially in pernicious vomiting, as demonstrated by Ewing [104] and Williams.[105] Furthermore, Gottschalk [106] has found, by means of the levulose test for function of the liver, that there is a reduction in the utilization of sugar by the liver in the majority of cases of normal pregnancy. Thus, as has been remarked, during pregnancy the liver is in a state of unstable equilibrium, which may account for its susceptibility.

Bacterial Infection.—Attempts to establish a specific micro-organism as the cause of acute yellow atrophy have been made early and have been continued to a certain extent to the present day. In many instances, the diseased organs were found to be sterile on bacteriologic examina-

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102. Beatty, W. K.: A Case of Acute Atrophy of the Liver, New York M. Rec. **48**:274, 1895.

103. Hofbauer, J.: Die Graviditätsveränderungen, Samml. klin. Vortr., 1910, p. 586.

104. Ewing, J.: The Pathogenesis of the Toxemia of Pregnancy, Am. J. M. Sc. **139**:828, 1910.

105. Williams, J. W.: Pernicious Vomiting of Pregnancy, Bull. Johns Hopkins Hosp., 1906, vol. 17.

106. Gottschalk, A.: Ueber den intermediären Kohlehydratstoffwechsel in der Schwangerschaft, Klin. Wchnschr. **1**:551, 1922.

tion. In many others, a variety of micro-organism, especially bacilli and cocci, have been recovered; none of these, however, justified any definite conclusion. So far as I know, no one has claimed to have discovered any such specific germs. Also, a large number of cases of acute atrophy of the liver have been observed to occur in the course of many infectious diseases such as osteomyelitis (Meder), erysipelas (Jehle [107] and Giulini [108]), purulent salpingitis (Sternberg), sepsis (Babes), gonorrhea (Weitz [109]), typhoid fever (Eppinger, Sr., and Dörfler), pneumonia (Hlava), diphtheria (Cahn [110]), appendicitis (Fischer,[111] Holländer [112] and Behrend; [113] the case of the last author was probably largely due to delayed chloroform poisoning) and several other infections. All such infections, inconstant as they are, and accidental as they may appear, in the light of Opie's [114] work cannot be disregarded as possible etiologic factors. Opie's experiments show that the activity of a hepatic poison may be so intensified by bacterial infections that a quantity of the poison which alone produces light changes may, in combination with the bacteria, cause destruction of almost the entire hepatic parenchyma. In fact, by the combination of such a hepatic poison as chloroform with *B. coli* or *Streptococcus pyogenes,* Opie has been able to reproduce in animals conditions which closely resemble acute yellow atrophy. That metabolic hepatic poisons similar in their action to chloroform or phosphorus may occur in man is well known, from the necrosis of the liver often seen in the toxemia of pregnancy as stated before and also from the great susceptibility in pregnancy to acute yellow atrophy. One cannot, therefore, be at all certain that the infections in the cases reported did not have some influence in the causation of the acute atrophy.

The association of acute atrophy of the liver with cases of so-called Weil's disease (infectious jaundice due to *Spirochaeta icterohaemorrhagiae* is even more pertinent. According to Pick,[115] pictures of acute

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107. Jehle: Allg. Wien. med. Ztg., 1898, p. 327, cited by Herxheimer.

108. Giulini: Ueber akute gelbe Leberatrophie, etc., Inaug. Diss., Munich, 1904, cited by Herxheimer.

109. Weitz: Ein Fall von akut verlaufender Gonococcaemie mit akuter gelber Leberatrophie, Med. Klin. **8**:192, 1912.

110. Cahn, J.: Akute Leberatrophie nach Diptherie des Magens, Deutsches Arch. f. klin. Med. **34**:113, 1894.

111. Fischer, W.: Akute gelbe Leberatrophie bei Syphilis, Berl. klin. Wchnschr. **45**:905, 1908.

112. Holländer, E.: Icterus bei Perityphlitis, Berl. klin. Wchnschr. **47**:1011, 1910.

113. Behrend, M.: Acute Yellow Atrophy of the Liver Complicating Acute Appendicitis, New York M. J. **114**:709, 1921.

114. Opie, E. L.: On the Relation of Combined Intoxication and Bacterial Infection, J. Exper. Med. **12**:367, 1910.

115. Pick, L.: Zur Pathologie des infectiösen Icterus, Berl. klin. Wchnschr. **54**:451, 1917.

yellow atrophy may sometimes be seen in Weil's disease, and Herxheimer states that the occasional occurrence of the two conditions together is not to be doubted, yet there is no mention of cases of acute yellow atrophy in the report of Dawson, Hume and Bedson,[116] who must have seen a great number of cases in the epidemics they studied in France during the Great War. Judging from the description of the pathologic changes in the liver by the authors named in the foregoing and by Garnier and Reilly,[117] Beitzke[118] and others, there is no resemblance in the lesions of the two conditions, so that a direct connection, i. e., a specific responsibility of *Spirochaeta icterohaemorrhagiae* for the acute yellow atrophy, is hardly to be suspected.

In the search for a specific micro-organism as the exciting agent of acute yellow atrophy, the thought that it might be due to some form of spirochete in analogy with Weil's disease and yellow fever was interesting. In connection with this, the case of Hayashi and Kibata[119] may be mentioned. These authors have reported a typical case of acute yellow atrophy in which they have found in the liver and in other affected organs what appeared to be stages in the life cycle of a species of spirochete. The organisms were present in abundance and, judging from the photographs, it is difficult to deny the presence of a spirochetal organism in that case. So far as I know, nothing similar has been seen before or since, in spite of assiduous search.

Syphilis.—The association of acute atrophy with syphilis is prominent and of great importance. It has long been known to clinicians that in its early stage syphilis may produce a form of benign jaundice, but this is rare, occurring in about 0.3 per cent of cases, according to Rolleston;[120] the lesions of acute atrophy occur more rarely. Viewed from the other side, acute yellow atrophy is found associated with syphilis with striking frequency. Altogether, there are about 700 reports of cases of acute yellow atrophy published in the literature to date. According to the estimation of Herxheimer from 130 to 150 of these were combined with syphilis, and almost always in the second stage of that disease. To be sure, in the cases reported in recent years many of the patients have been treated with arsphenamine, which may in itself bring about acute yellow atrophy. Even before the advent of arsphena-

116. Dawson, B.; Hume, W. E., and Bedson, S. P.: Infective Jaundice, Brit. M. J. **2**:345, 1917.

117. Garnier and Reilly: Les ictères graves primitifs, Presse méd. **27**:641, 1919.

118. Beitzke, H.: Ueber die pathologische Anatomie der ansteckenden Gelbsucht, Berl. klin. Wchnschr. **53**:188, 1916.

119. Hayashi, N., and Kibata, T.: Spirochetal Organisms in Tissues in Acute Yellow Atrophy of the Liver, J. Infect. Dis. **30**:64, 1922.

120. Rolleston, H. D.: Discussion on Degenerative Diseases of the Liver, Brit. M. J. **2**:1055, 1922.

mine, Fischer had collected reports of fifty cases of syphilis, Parkes Weber, fifty-three, as quoted by Rolleston, and Herxheimer, sixty-nine; in 1914, Michael [121] figured that 10 per cent of the cases in the published reports were associated with syphilis. Against the objection that in prearsphenamine days the mercury might have been the responsible factor, it may be pointed out that there are also cases on record in which antisyphilitic treatment had not been instituted, as in the recent case of Graef.[122] At any rate, the influence of syphilis in acute yellow atrophy is universally recognized, but whether syphilis alone, or better, whether *Spirochaeta pallida* or its toxins is, under certain circumstances, capable of producing the specific change, does not appear settled. Herxheimer and Gerlach and Herxheimer seem to think that the syphilis in such cases is directly responsible, and they point out that most of the cases presenting a syphilitic etiology belong to the subacute variety. English authors, among them Rolleston, are not convinced of it. MacDonald [123] has studied five cases in which arsphenamine and mercury had been used. Cultures from the organs made postmortem yielded bacilli of the coli-typhoid group in all the five cases. MacDonald therefore holds that the infection represented a factor which, added to a liver already damaged by syphilis and probably also by arsenic and mercury, had brought about the changes of acute atrophy.

Infectious or Epidemic Jaundice.—Acute atrophy seems to have occurred in epidemics of jaundice in early times (Hirsch [124]). In one epidemic on the island of Martinique in 1858, twenty pregnant women died from what appeared to be acute yellow atrophy. In an epidemic in the prison of Gaillon in 1859, one patient died of acute yellow atrophy, with characteristic postmortem changes. In recent years waves of jaundice have occurred in Germany, Holland, Sweden and the United States, and the increase in the incidence of acute yellow atrophy has been a matter of general remark. Incidentally, the jaundice caused by syphilis and arsphenamine appeared to have increased and with that the acute yellow atrophy that sometimes follows these conditions. There was at first a tendency to ascribe the rise in the jaundice and the acute atrophy to the increase in syphilis and to the treatment with arsphenamine, but this did not explain the rise among nonsyphilitic people.

121. Michael, M.: Der Icterus syphiliticus praecox unter besonderer Berücksichtigung der dabei auftretenden akuten gelben Leberatrophie, Arch. f. Dermat. u. Syph. **120**:694, 1914.

122. Graef, H.: Akute Leberatrophie bei sekundarer Lues, Deutsche med. Wchnschr. **35**:1925, 1909.

123. MacDonald, S.: Acute Yellow Atrophy in Syphilis, Brit. M. J. **2**:76, 1918.

124. Hirsch, A.: Handbook of Geological and Historical Pathology, vol. 3, p. 417; trans. from the German by Charles Creighton, London, The New Sydenham Society, 1886.

In Germany, it was first thought that it might have something to do with the poor nutrition of the period immediately after the war. But this again did not explain the increase of jaundice in other countries. In this country, Stokes, Rudeman and Lemon [125] of the Mayo Clinic have studied the question of the relationship of the frequent occurrence, with occasional fatal result, of jaundice in relation to syphilis or treatment with arsphenamine. Jaundice as a complication of the treatment of syphilis in the Mayo Clinic was a relatively rare occurrence during the period from August, 1916, to August, 1918, but from August, 1918, to July, 1920, the incidence of this complication had increased more than 1,000 per cent; yet neither the arsphenamine nor the technic of administration had changed. However, no definite time sequence between the administration of arsphenamine and the incidence of jaundice could be detected, and there was no constant relationship between the doses of arsphenamine administered and the severity of the hepatic symptoms. For these and many other good reasons, the experimenters were able to conclude that the increase of jaundice in their cases was due to the prevalence of an infectious jaundice. One fourth of the patients gave histories of jaundice developing in their localities, often in relatives, neighbors and friends.

Previous to this, Symmers [126] called attention to the existence of an epidemic of jaundice in New York City (1919-1920), of which he was able to study sixteen cases. Clinically and anatomically, the disease presented features which, on the one hand, were strikingly similar to those of infectious jaundice and yellow fever and on the other to acute yellow atrophy. All attempts to demonstrate spirochetes failed. Of the sixteen patients, nine died, and necropsy in six of these showed changes in the liver which ranged from cloudy swelling to widespread necrosis, corresponding in all essentials to acute yellow atrophy.

In the period between 1920 and 1923, many epidemics were observed in different parts of this country, particularly in New York State In the report of Williams,[127] an account of the epidemic in New York State is given for the period between 1921 and 1922. During the same period, Dr. Irving P. Lyon and I had an opportunity to study an epidemic in the neighboring town of Alden, N. Y. In fourteen cases the results of the bacteriologic work, which included experiments with guinea-pigs with blood and urine in various stages of the disease were.

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125. Stokes, J. H.; Rudeman, R., and Lemon, W. S.: Epidemic Infectious Jaundice and its Relation to the Therapy of Syphilis, Arch. Int. Med. **26**:520 (Nov.) 1920.

126. Symmers, D.: Epidemic Acute Hemorrhagic Jaundice of Toxic Origin, J. A. M. A. **74**:1153 (April 4) 1920.

127. Williams, H.: Epidemic Jaundice in New York State, J. A. M. A. **80**:533 (Feb. 24) 1923.

like the results of Symmers, of the New York State Board of Health, and those of Blumer [128] in New Haven, totally negative.

According to Williams there were no direct fatalities, but an unusual number of cases of acute yellow atrophy sprang up in Buffalo. While in our hospital the necropsy records for several years previous to the epidemic do not show a single case of acute yellow atrophy, seven such cases occurred in a period between 1921-1923.

In Germany, Ruge [129] among others has analyzed the matter of the increase in jaundice. From his paper, too, it appears clearly that an infectious nonspirochetal jaundice was largely responsible for the wave in that country. The belief is gradually gaining ground in this country as well as abroad that so-called catarrhal jaundice is, as Blumer expresses it, merely the sporadic type of infectious jaundice. Whether this is so or not, there is hardly any dissention from the opinion as held by Minkowski,[130] Umber,[60] Geronne, Hart,[131] Strümpell,[132] Blumer and many others that both may develop into acute yellow atrophy.

Phosphorus Poisoning.—Following Rokitansky's description of acute yellow atrophy, there was a period in which most cases showing the picture of icterus gravis were regarded, especially in Vienna, as acute yellow atrophy regardless of whether the liver was atrophic or not Rokitansky himself had published a report of three cases in which the liver was enlarged and showed a great accumulation of fat. But as he had looked on the fatty changes—"the steatosis"— in the liver and kidney as an essential feature in acute yellow atrophy, he did not hesitate to identify these cases with that disease, in spite of the fact that in one of them there was a history of poisoning with phosphorus However, von Hauff [133] later (1861) called attention to the association of the large fatty liver with phosphorus poisoning, and later this was confirmed experimentally by Lewin and Ehrle.[134] There were many cases of phosphorus poisoning in that period. Phosphorus was in vogue both as a suicidal agent and as an abortive, for which purpose a

128. Blumer, G.: Infectious Jaundice in the United States, J. A. M. A. **81**:353 (Aug. 4) 1923.

129. Ruge, H.: Einfacher catarrhalischer Icterus und Icterus nach Salvarsan, Ztschr. f. klin. Med. **101**:684, 1925.

130. Minkowski, O.: Die nosologische Stellung der akuten gelben Leberatrophie, Med. Klin. **17**:491, 1920.

131. Hart, C.: Ueber die Beziehungen des icterus infectiosus zur akuten Leberatrophie, und Lebercirrhose, München. med. Wchnschr. **64**:1598, 1917.

132. Strümpell, A.: Ueber Icterus, Deutsche med. Wchnschr. **47**:1219, 1921; München. med. Wchnschr. **68**:1133, 1921.

133. Von Hauff: Tod durch Phosphorpaste, Med. Cor.-Bl. f. d. Württ. Arzte **30**:265, 1860, cited by Herxheimer.

134. Lewin, L., and Ehrle, E.: Fruchtabtreibung durch Gifte, ed. 2, Berlin, A. Hirschwald, 1904, p. 224.

milk emulsion of the heads of matches would often be used. Thus it did not take long to learn the anatomic changes, and it was soon discovered that the more protracted cases showed changes in the liver often indistinguishable from acute yellow atrophy.

The outstanding feature in the pathologic changes in the liver in phosphorus poisoning is a fatty infiltration whereby the liver becomes enlarged, and correspondingly of a marked yellow. But, on the one hand, when the dose has been sufficiently large the patient may die before the changes in the liver develop and, on the other hand, when the poisoning is less severe and the course longer, the liver may be small and may show the picture of acute yellow atrophy. The fatty changes usually take place rapidly, as can be seen from experimental work, especially that of Cornil and Brault.[135] The rapidity may, of course, vary with the dose, the previous state of the liver and other factors, but high grade fatty metamorphosis with great enlargement may develop in from six hours (Winiwarter [8]) to two days (Miura [136]). Death occurs much earlier than in acute yellow atrophy. In rare cases, it may occur on the first day (Lewin and Hessler [137]). Most commonly, however, it takes place within the first week, when the liver exhibits the typical fatty changes (Lewin, Meischner [18] and von Jaksch [138]). Many patients live longer (up to seventeen days), and the later they die the most likely the liver is to be in a state of atrophy, with pictures of red and yellow atrophy combined. The transformation of the large fatty liver into the small atrophic one takes place with great rapidity, the change sometimes occurring in one day. Finally, some patients may continue to live and develop a coarsely nodular cirrhosis (Paltauf).

Microscopically, the early lesion is represented by the accumulation of fat in the parenchymatous cells of the liver. This is of the highest grade, most of the cells appearing extremely distended with large fat droplets. The process begins, according to the majority of observers, in the periphery of the lobule, progresses rapidly toward the center, and soon involves the entire lobule. The question as to the nature of the accumulation of fat, whether it is a degenerative or infiltrative process, has lost its importance, since from experimental work, especially

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135. Cornil, V., and Brault: Recherches histologiques relatives a l'etat du foie, du rein et du poumon dans l'empoisonnement par le phosphore et par l'arsenic, J. de l'anat. et de la phys. **18**:1, 1882.

136. Miura, I. M.: Die Wirkung des Phosphors auf den Fötus, Virchows Arch. f. path. Anat. **96**:54, 1884.

137. Hessler, H.: Ueber den Tod durch akute Phosphorvergiftung vom gerichtsärztlichen Standpunkt, Vrtljschr. f. gerichtl. Med. **35**:248, 1882.

138. Von Jaksch, R.: Beitrage zur Klinik der akuten Phosphorvergiftung des Menschen, Deutsche med. Wchnschr. **19**:10, 1893.

that of Rosenfeld, it is assumed that in all instances of fatty degeneration the fat is mostly transported to the cell. The fatty change is followed by a disintegrating process of the cell, much like that which occurs in acute yellow atrophy. Whether this also begins in a definite zone of the lobule is questionable, judging from the different descriptions in phosphorus poisoning in man as well as in experimental animal material. Phenomena of regeneration are here too observed early in the form of mitotic figures in the surviving liver cells and bile duct proliferation.

Besides the changes in the liver, fatty changes are found in the kidneys, sometimes associated with necrosis in the proximal convoluted tubules and in the myocardium and striped muscle fibers, especially those of the adductors, psoas, gastrocnemii, tongue and diaphragm; and fatty changes of the gastric glands and, according to Herxheimer, also fatty degeneration of the vascular endothelium. The spleen is usually slightly enlarged and soft, and hemorrhages are conspicuous in the serous membranes, lungs, muscles and in many other places. Here, too, the coagulability of the blood is diminished as a result of the loss of fibrinogen, and moderate polycythemia may be present, as reported by von Jaksch and Taussig.[139]

Chemical examination of the liver gives essentially the same results as in acute yellow atrophy. The most prominent difference is found in the greater increase in fat in the liver in poisoning by phosphorus, the fat being three times the normal amount as compared with the liver of acute atrophy, in which the fat is only slightly increased or not increased at all. Riess,[140] who has compared the thirty-six cases of phosphorus poisoning and fourteen cases of acute yellow atrophy, states that the total nitrogen is materially reduced in both conditions. In phosphorus poisoning the presence of peptone-like extractives and sarcolactic acid was marked, while in acute atrophy little of these products was present. The presence of leucin and tyrosin is not the rule. In the thirty-six cases of Riess, tyrosin was missing twenty-nine times, and according to Wells leucin is even less frequently found. Wells [84] considers it possible that the fatty changes produced by phosphorus are due to its action especially on the oxidizing ferments, leaving the autolytic enzymes and the lipase free to digest the cell and to form fat. Herxheimer connects the fatty metamorphosis with the loss of glycogen in the liver cell, as demonstrated by Rosenfeld.[141] It is frequently stated that the action of phosphorus compared with acute atrophy is more general, acting on all the organs alike. In the case of poisoning with phosphorus many of the clinical phenomena must

139. Taussig, O.: Ueber Blutbefunde bei akuter Phosphorvergiftung, Arch. f. exper. Path. u. Pharmacol. **30**:161, 1892.

140. Riess, L.: Berl. klin. Wchnschr. **57**:537, 1920.

141. Rosenfeld, G.: Der Process der Verfettung, Berl. Klin. Wchnschr. **41**:587 and 617, 1904; **43**:978, 1906; **44**:1663, 1907.

equally be due to impairment of the function of the liver, especially in the later stages.

At any rate, it can be seen that the action of phosphorus on man may bring about a disease that has a striking similarity to acute yellow atrophy. In fact, the clinical and anatomic pictures are often so much alike that in earlier periods it was suspected by Paltauf that poisoning with phosphorus was the cause of many a case of acute yellow atrophy, in spite of the negative histories, and Kobert [142] suggested that acute yellow atrophy might be due to the liberation of phosphorus from its organic combinations during the course of certain gastro-intestinal intoxications. Nevertheless, certain differences in the two conditions are generally recognized. In the early stages these are apparent anatomically, as, instead of being atrophic, the liver is markedly large and outspokenly fatty. But even chemically, before the process of disintegration is well on its way, the split products of protein metabolism will not be so readily demonstrable in the urine and blood. Histologically, too, many have insisted that the distinction could be made between the two processes from the site in which the changes begin. It may be true that there is no regularity with regard to the zone of the lobule in which the process begins in acute yellow atrophy—that it may sometimes be peripheral and at other times central—but in phosphorus poisoning most observers are convinced that the changes begin in the periphery of the lobule. Above all, as was emphasized by Marchand, Anschütz [143] and Paltauf, the changes in phosphorus poisoning are predominantly fatty, while those in acute atrophy are predominantly necrotic. Furthermore, in phosphorus poisoning it is primarily the cytoplasm that is attacked, while the nucleus remains intact for a long time. In acute atrophy, as Anschütz expresses it, the life of the cell is hit, the necrosis beginning with the nucleus.

Chloroform Poisoning.—Ever since the introduction of anesthetics, it has been known that fatal results may sometimes follow chloroform anesthesia. However, it was not until later that the condition now well known as delayed chloroform poisoning was recognized. Such cases were reported by Bastianelli [144] (1890), Fraenkel [145] (1892), Guthrie [146] (1894) and Bandler [147] (1896). The last named author

142. Kobert, R.: Lehrbuch der Intoxicationen **2**:286, 614, 1906.

143. Anschütz, W.: Vergiftung und akute gelbe Leberatrophie, Arb. a. d. Path. Inst. Tübingen **3**:230, 1899.

144. Bastianelli, R.: Sulla morte tardiva per cloroformio, Bull. di Soc. Lancisiana di osp. di Roma, 1891, p. 325.

145. Fraenkel, E.: Ueber Chloroformnachwirkung beim Menschen, Wirch. Arch. **129**:254, 1892.

146. Guthrie, L. G.: Some Fatal After Effects of Chloroform on Children, Lancet **1**:193, 1894; **2**:583, 1905.

147. Bandler, V.: Ueber den Einfluss der Chloroform und Aethernarkose auf die Leber, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **1**:303, 1896.

pointed out clearly the effect of chloroform on the liver, which may vary from insignificant lesions to total destruction of the organ, leading to acute yellow atrophy. In fact, Stocker had reported a case under the title of acute yellow atrophy which, as soon became evident, was really one of delayed chloroform poisoning. There are reviews on this subject by Bevan and Favill [148] (1905) and by Guleke [149] (1907). In 1924, Herxheimer found seventy cases reported in the literature, to which he added twelve of his own. It is important to note that the deaths from chloroform have occurred mostly after abdominal operations (the most important of which is appendicitis), especially in regions drained by the portal vein; that alcoholism, previous disease of the liver, various infections and repeated chloroform narcosis predispose to the accident, and that most often it occurs in young individuals.

The clinical manifestations begin after a period of latency, the so-called incubation period, of from twenty-four to thirty-six hours following the operation. Icterus appears gradually; then restlessness and vomiting set in, followed by convulsions and coma. Death usually ensues in from two to four days, rarely on the fifth day. When death occurs early, at necropsy the liver is found to be large, soft, yellow and bile-stained. Microscopically, there are found high grade fatty changes and there may be necrosis of the central zone of the lobules. When death occurs after a few days the picture may resemble acute yellow atrophy, the liver being mottled red and yellow and the lobules on cut surface red in places and sunken in the center, and yellow and elevated in the periphery. Microscopically, while in the periphery some cells may still be preserved though markedly infiltrated with fat, the central parts of the lobule are completely broken down, and there is left a granular detritus containing fat droplets mixed with red blood corpuscles, leukocytes and lymphocytes. There may also be found round cell infiltration and connective tissue proliferation in the portal spaces. The beginning of the process in the central zone of the lobule is emphasized in most of the reports. Besides the changes in the liver, there are found fatty changes with occasional necrosis in the kidney, fatty changes in the heart, in the skeletal muscles, and in the gastric glands, and hemorrhages in the serous membranes and in the gastro-intestinal mucosa. Thus here, too, the liver shows the lesion of importance, and death is largely brought about by liver insufficiency. Chemically, Wells has found a loss of one third of the solids in the liver in from three to four days, which was indicated by the presence of free amino-acids, purins, peptones and polypeptids. He also states that there is

148. Bevan, A. D., and Favill, H. B.: Acid Intoxication and Late Poisonous Effects of Anesthetics, J. A. M. A. **45**:691 (Sept. 2) 1905.

149. Guleke, N.: Akute Gelbe Leberatrophie im Gefolge der Chloroformnarkose, Arch. f. klin. Chir. **83**:602, 1907.

less replacement of protein by water and more fatty infiltration than in acute yellow atrophy. Here, too, a loss of glycogen has been demonstrated (Arnheim [150] and Herxheimer).

Experimental studies have also been made, especially on dogs. Among the later ones may be mentioned the work of Whipple and Sperry,[151] Howland and Richards,[152] Opie and Muskens.[153] The changes in the animals are strikingly similar to those in man. The sequence of the changes, as studied on animals, are described by Herxheimer somewhat as follows: First, there occurs infiltration of the capillary endothelium with fat. This is followed by accumulation of fat in the parenchymatous cells, at first nearer the periphery, although the outermost layer of cells is free from fat. The cytoplasm of the cells in the central zone assumes a hyaline appearance; the nuclei become pyknotic, begin to break down and finally dissolve, disappearing and leaving only a detritus mixed with fat globules. The peripheral part may still show well-preserved cells which are filled with fat. The capillaries in the necrotic areas become dilated and between them lies the detritus filled with red blood corpuscles, leukocytes and lymphocytes. Furthermore, spindle cells appear, and also bile pigment and bile thrombi. Thus, one finds again the picture of acute yellow atrophy. The removal of the débris begins early, and mitotic and amitotic figures soon become conspicuous. The bile capillaries do not show any proliferation. With regard to the fatty changes, chloroform poisoning stands intermediate between phosphorus and acute yellow atrophy, according to Wells.

Mushroom Poisoning.—A series of interesting papers on the subject of mushroom poisoning has been published by Ford.[154] In these the botanical, clinical, pathologic and pharmacologic aspects of the subject, as well as an interesting history, are presented. It appears that of the many varieties of poisonous mushrooms, *Amanita phalloides,* or deadly amanita, and *Amanita verna* are most commonly taken and that in their action they closely resemble phosphorus. Mushroom poisoning was

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150. Arnheim, J.: Ueber den Einfluss der Chloroformnarkose auf den Blutzuckergehalt, etc., Wien. klin. u. therap. Monatschr. **2**:1078, 1905.

151. Whipple, G. H., and Sperry, J. A.: Chloroform Poisoning. Liver Necrosis and Repair, Bull. Johns Hopkins Hosp. **20**:278, 1909.

152. Howland, John; and Richards, A. K.: An Experimental Study of the Metabolism and Pathology of Delayed Chloroform Poisoning, J. Exper. Med. **11**:344, 1909.

153. Muskens, A. L. M.: Klinischer und experimenteller Beitrag zur Kenntnis des Chloroformspättodes, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **22**:568, 1910-1911.

154. Ford, W. W.: Toxicological Constituents of Amanita Phalloides, J. Exper. Med. **8**:437, 1906; Toxins and Antitoxins of Poisonous Mushrooms (Amanita Phalloides), J. Infect. Dis. **3**:191, 1906.

recognized by the ancients; it still occurs in many countries, and in this country reports have been published on the subject by Förster,[155] Trask[156] and McIlvaine.[157] Ford estimates the total number of cases reported in the literature to be more than 300. An active principle, a hemolytic substance named phallin, first isolated by Kobert, was shown by Ford to be relatively harmless to man, unless it is insufficiently boiled, for it is destroyed by a temperature of more than 70 degrees, and also by acids and pancreatic juice. This substance—a glucosid, as determined by Abel and Ford—when injected into animals produces hemoglobinuria and multiple hemorrhages. The main action was shown by Ford to be due to a substance closely allied to indol or pyrrhol derivatives, the "amanita-toxin." When injected into animals, this gives rise to changes analogous to those in man. The symptoms in mushroom poisoning appear after a period of latency varying from six to fifteen hours and consist of violent abdominal pain, diarrhea, vomiting of blood, hemoglobinuria, and finally anuria, jaundice and cyanosis and rarely convulsions and coma. The mortality ranges from 60 to 100 per cent, the patients dying in from two to four days, rarely after six days. At necropsy, the liver is found to be enlarged and the seat of high grade fatty metamorphosis. In later stages the picture approaches that of acute yellow atrophy as was seen in the case of Schmidt, in which the patient died on the sixth day. Careful microscopic studies are to be found in the publications of Schmidt[158] and Fraenkel.[159] The changes seem to be identical with those of phosphorus poisoning. For the beginning of the process the central zone of the lobule is usually emphasized, although in some cases the changes were uniformly distributed over the lobule and in others an intermediate zone seemed to be affected. Besides, there are fatty changes in the kidneys and in the heart and voluntary muscles. In Schmidt's cases, the kidney showed changes resembling bichloride poisoning. Here, too, fatty changes in the glands of the stomach were demonstrable, as well as fatty changes in the alveolar epithelium of the lungs and in the vascular endothelium, and, furthermore, hemorrhages in the serous membranes and in the gastro-intestinal mucosa. The resemblance to phosphorus poisoning is apparent from the various descriptions,

155. Förster, E. J.: Mushrooms and Mushroom Poisoning, Boston M. & S. J. **123**:267, 1890.

156. Trask, J. D.: Cases of Mushroom Poisoning, Am. J. M. Sc. **85**:358, 1883.

157. McIlvaine, C.: Amanita Toxin and Its Antidote, M. and S. Reporter, Philadelphia, **53**:684, 1885.

158. Schmidt, M. B.: Pathologisch-anatomische Veränderungen nach Pilzvergiftung, Ztschr. f. ang. Anat. u. Konstitutionslehre **3**:146, 1918.

159. Fraenkel, E.: Knollenblätterschwamvergiftung, München. med. Wchnschr. **67**:1193, 1920.

although the beginning lesion in point of lobular topography resembles more the one in chloroform poisoning. Tappeiner [160] estimates the fat content of the liver in mushroom poisoning at 53.6 per cent, as compared with the fat content of phosphorus poisoning of from 50 to 70 per cent. A great deal more could be said on the subject of mushroom poisoning, but it was only necessary to show that in certain mushrooms a poison exists which may produce in man a condition similar to acute yellow atrophy.

Other Hepatic Poisons.—Besides the poisons named in the foregoing, the following are known to produce conditions similar to acute yellow atrophy.

Arsenic: Experiments on animals by Cornil and Brault, Podwyssozki and many others show the marked resemblance of the action of this poison to that of phosphorus. Herxheimer states that the same is true of arsenic poisoning in man and cites a case of his own in which the liver at necropsy showed the picture of subacute yellow atrophy. In view of the evidence one has about the effects of arsenic, it is difficult to ignore this component in arsphenamine poisoning. Yet as Stewart [161] points out, there are several other substances producing the same lesions which, in common with arsphenamine, contain a benzene radical, so that the arsenic need not, at least not entirely, be responsible. Thus the question of the influence of arsphenamine on the acute yellow atrophy sometimes following its administration for syphilis seems even more complicated.

Mercury: It is often stated that mercury may give rise to acute yellow atrophy, but this seems to be based on experiences with it in the treatment of syphilis. Still, syphilis alone as stated in the foregoing, is an important factor. Tileston [162] reported a case of acute yellow atrophy (case 2) in mercurialism without syphilis.

Picric Acid, Trichlorethane, Trinitrotuluene and Dinitrobenzol.—A case of poisoning with picric acid is reported by Pauly, as quoted by Rolleston. The last three substances have been particularly studied in England during the Great War by Wilcox,[163] Spilsbury,[164] Turnbull [165] and Stewart.[161] The patients were workers in the airplane industry

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160. Tappeiner, cited by Ford.

161. Stewart, M. J.: Toxic Jaundice in Munition Workers and Troops, Brit. M. J. **1**:156, 1917; Lancet **1**:153, 1917; Brit. M. J. **2**:584, 1920.

162. Tileston, W.: Acute Yellow Atrophy, Boston M. & S. J. **158**:510, 1908.

163. Wilcox, W. H.: Discussion of Degenerative Diseases of the Liver, Brit. M. J. **2**:1055, 1922; Lancet **196**: 868 and 942, 1919.

164. Spilsbury, B. H.: Toxic Jaundice in Munition Workers and Troops, Brit. M. J. **1**:156, 1917; **2**:583, 1920.

165. Turnbull, H. N.: Toxic Jaundice in Munition Workers and Troops, Brit. M. J. **1**:156, 1917.

(tetrachlorethane) or in munition factories (dinitrobenzol and trinitrotoluene), who developed toxic jaundice mostly after they had been removed from the influence of the chemicals. The pictures presented at necropsy were mostly those of subacute yellow atrophy (Spilsbury).

Several other substances, among which are apparently harmless drugs, have occasionally been held responsible for acute atrophy of the liver. One of these is male-fern. Meier [166] has reported a case of acute yellow atrophy following a course of a 10 per cent extract of male-fern in oil to expel a tape-worm. The total dose had been twice that given in the directions on the box of "Filmaronöl." The patient died on the sixth day, and necropsy revealed acute yellow atrophy. However, the liver was already the seat of extensive syphilitic changes

The other substances are theacylon and caseosan, both as quoted by Herxheimer; and Zieler and Birnbaum [167] have reported two cases following treatment with yatren. Finally, von Bein [168] describes a case of acute yellow atrophy following the inhalation of fumes of hydrocyanic acid.

Lastly, it may be mentioned that acute yellow atrophy occasionally occurs in sheep and sometimes also in goats, oxen and horses in the form of so-called acute lupinosis, in certain districts of northern Germany in which lupinus (flavus caeruleus or albus) is used as fodder, the disease being caused by certain poisonous forms of lupinus. A similar disease, according to Hutyra and Marek,[169] occurs in the vicinity of New Orleans, La., by a bean-like forage plant, *Mucuna utilis* (velvet bean). The disease also occurs in horses in South Africa as reported by Theiler [170] as a result of poisoning with certain forage plants, the action being similar to that of the senecio toxin.

COMMENT

It has been seen that the peculiar condition of the liver in acute yellow atrophy is brought about by an intense destructive process of the liver cells, generally recognized as autolysis. There are also associated lesions in other organs which are probably largely due to systemic intoxication, resulting from hepatic insufficiency and partly also perhaps to the action of the same substance that affects the liver.

166. Meier, M.: Akute gelbe Leberatrophie, Ztschr. f. Klin. Med. **92**:406, 1922.

167. Zieler, F., and Birnbaum, G.: Akute gelbe Leberatrophie nach Yatren, München. med. Wchnschr. **69**:664, 1922.

168. Von Bein, G. V.: Atrophy of the Liver after Inhalation of Hydrocyanic Acid, Zentralbl. f. inn. Med. **45**:937, 1924; abstr. in J. A. M. A. **84**:241 (Jan. 17) 1925.

169. Hutyra, F., and Marek, J.: Special Pathology and Therapeutics of the Diseases of Domestic Animals, Chicago, A. Eger, 1926, vol. 2, p. 443.

170 Theiler, cited by Hutyra and Marek.

It has also been seen that the action of a variety of extraneous poisons may give rise to autolysis in the liver and to changes in the organs resulting in pictures that are indistinguishable from acute yellow atrophy. Whether this justifies the frequently repeated saying that acute yellow atrophy is caused by known as well as unknown poisons is a debatable question. On analysis one first finds that it is only in later stages that the known poisons resemble idiopathic atrophy. In the early stage, when the liver is enlarged and fatty, it would be difficult, it seems, to mistake a case of phosphorus or chloroform poisoning for acute yellow atrophy. It is true that no one knows what the early appearance of the liver is in acute yellow atrophy; for in that disease, most of the patients die after several weeks, by which time a liver in a case of phosphorus poisoning also becomes atrophic. Moreover, some of the early cases of acute atrophy apparently did show enlargement of the liver, and besides there are no means of determining the beginning of the process in acute yellow atrophy. Nevertheless, if one considers that idiopathic atrophy, whether it is due to an infection or an endogenous poison, is more likely to be a progressive process than a condition caused by a single dose of poison, it may, after all, be possible to compare the nature of the two lesions. In fact, even in the oldest cases of idiopathic atrophy the initial process may be detected in the regenerated cells, and in the average case one hardly misses areas of yellow atrophy. In other words, it is not the duration of the disease, but the age of the lesion that one should compare, but by doing so, one finds an outstanding difference in the early changes in the liver. The difference has already been pointed out in the foregoing, and I need only emphasize here the prominence of the fatty changes in the cases of poisoning as compared with idiopathic atrophy. It is usually recognized that the necrosis of the cells following the action of the known poisons is preceded by an accumulation of fat in the cytoplasm. Possibly this is the result, as Herxheimer points out, of a primary loss of glycogen in the liver cells. In idiopathic atrophy, however, necrosis, as far as can be determined, is the first event in the process. At any rate, fatty metamorphosis in acute yellow atrophy is only prominent in the older descriptions when it was confused with phosphorus poisoning, and chemical analysis of the liver bears out the present impression that it is not an important factor.

On the other hand, attempts to make distinctions in these conditions on the basis of the lobular topography of the necrosis have not been of much help. Within the group of poisons, there are some that show a more or less constant seat of necrosis, as, for instance, chloroform (central) or phosphorus (peripheral), but in acute atrophy this seems to vary considerably, not only in the different cases but also in the same liver. The greater severity of the changes in the rest of the body in

cases of poisoning cannot be held out as an important distinguishing mark, as this may be only a quantitative difference; and it may well be, as is often stated, that because of the greater initial damage to the organs, such as the kidney or heart, the patients usually do not survive long enough to develop the atrophic liver.

The difference in the early changes, as pointed out in the preceding paragraph, seems sufficient ground for many authors, among them Marchand, Paltauf, Herxheimer and Wells, to maintain a more or less sharp distinction between idiopathic atrophy on the one hand and the atrophy due to the well known poisons on the other. On the other side, there is a tendency, especially among clinicians, not only to disregard the histologic distinctions but also to deny any specificity to the condition called acute yellow atrophy. Thus, Eppinger says that all poisonous substances which acting relatively mildly, may cause only a parenchymatous hepatitis must, under favorable circumstances, be able to produce acute yellow atrophy. He bases this chiefly on the fact that in many conditions in which the liver is the seat of a parenchymatous degeneration the well known focal necroses, such as have been studied by Mallory, are often encountered; he regards this as a step farther toward the autolytic process. For this reason, Eppinger thinks that it is not surprising that a case of acute yellow atrophy sometimes develops on the basis of such infections as osteomyelitis, sepsis and erysipelas. A similar view is held by Minkowski, who regards acute yellow atrophy as a severe form of acute diffuse hepatitis and includes it with the other conditions of the liver associated with jaundice or without it, and with chronic diffuse hepatitis in the form of cirrhosis of the liver. According to Minkowski, it may be due to a variety of exogenous and endogenous toxic and infectious agencies originating from the blood and bile vessels and bringing about all those degenerative and proliferative processes which in the wider sense of the word are designated as inflammatory. In other words, there is no specificity in the action of either the known poisons or the unknown ones. The process of autolysis which amounts to a necrobiosis of the cell combined with a prominent activity of its autolytic ferments does not, in fact, seem to be extraordinary, judging from the resistance of ferments in general. An autolytic process, it is thought, can be induced by almost any injurious substance acting on the liver, providing the action is sufficiently intense. Nevertheless, Minkowski admits that acute yellow atrophy takes a specific place in pathology because of the rapidity with which the disintegration takes place. This, he thinks, is rather a characteristic of the organ, as fermentative processes of a specific nature occur in the liver with an intensity not seen anywhere else. He compares it with the pancreas and its fat-necrosis.

It is clear that from this standpoint there is no difficulty in explaining the frequent occurrence of acute atrophy in syphilis, the accumulation of this condition in the course of epidemics of infective jaundice, during pregnancy, in cirrhosis of the liver and in all forms of infection. This would reduce the number of cases of so-called idiopathic atrophy to a minimum, for in most of those cases, if there is no other accompanying disease, there is frequently a period of mild jaundice preceding the onset of the severe symptoms which might very well be regarded as a catarrhal jaundice terminating in acute yellow atrophy as a result of the augmented action of the injurious substance. For cases that cannot be connected with any other disease, the purely cryptogenic forms, a gastro-intestinal poison is frequently assumed. Eppinger lays great stress on this possibility, thinking of the production of atypical products of digestion by an abnormal intestinal flora. There are other theories, but it seems useless to go into them since one can do no more than guess in this matter.[171]

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171. Other literature on acute yellow atrophy can be found in the articles of Thierfelder, Quincke, White and Herxheimer. The last-named article is the most recent, and gives the fullest review of the subject, and contains an enormous bibliography. The following articles may also be referred to: Abel, J. J., and Ford, W. W.: J. Biol. Chem. **2**:273, 1906-1907. Dörfler, H.: München. med. Wchnschr. **36**:878, 1889. Eppinger, H.: Allgemeine und spezielle Pathologie des Icterus, Spezielle Pathologie und Therapie innerer Krankheiten, von Brugsch und Krauss **6**:1, 1917. Ford, W. W.: Bull. Johns Hopkins Hosp. **18**:123, 1907; J. Infec. Dis. **5**:116, 1908. Fraenkel, E.: Virchows Arch. f. path. Anat. **127**:381, 1892. Hart, C.: Med. Klin. **17**:523, 1921. Mallory, F. B.: J. Med. Res. **6**:264, 1901. Ponfick, E.: Virchows Arch. f. path. Anat. **119**:193, 1890. Schmidt, R.: Inaug. Diss., Kiel, 1897, cited by Herxheimer. Schultze, H.: München. med. Wchnschr. **64**:806, 1917. Seyfarth, C.: Deutsche med. Wchnschr. **47**:1222, 1921. Stocker, S.: Centralbl. f. Gynäk. **19**:1181, 1895. Wagner, E.: Deutsches Arch. f. klin. Med. **34**:524, 1884. Umber, F.: Klin. Wchnschr. **1**:1585, 1922. Weitz: Klin. Wchnschr. **1**:2021, 1922. Wells, H. G.: J. Biol. Chem. **5**:129, 1907; Delayed Chloroform Poisoning and Allied Conditions, J. A. M. A. **46**:341 (Feb. 3) 1906. Williams, J. W.: Obstetrics, ed. 5, 1924, p. 587.

Notes and News

News of Societies.—At its meeting next year (Washington, May 1 and 2, 1928) the American Association of Pathologists and Bacteriologists will have as a selected and assigned topic "Nonsuppurative Diseases of the Kidney," which will be introduced with a general review by E. T. Bell of the University of Minnesota. Papers on this topic will be desired for the program.

The Seattle Academy of Surgery has established a service to collect and study data on inheritance of cancer in the community.

University News, Promotions, Resignations and Appointments.—James C. Small has been appointed director of the laboratory in the Philadelphia General Hospital to take the place of E. B. Krumbhaar who has accepted a professorship of pathology in the University of Pennsylvania.

John A. Kolmer, professor of pathology and bacteriology in the graduate school of medicine of the University of Pennsylvania, has received the degree of doctor of laws from Villanova College.

Walter Reed's Birthplace.—Belroi, Gloucester County, Virginia, where was born Walter Reed, who demonstrated the mosquito transmission of yellow fever, will be made into a permanent memorial by the Virginia Medical Society.

E. F. Scheidegger has resigned as resident pathologist at the hospital of the University of Nebraska School of Medicine in Omaha, and his place has been filled by Louis A. Frank.

George H. Whipple, dean and professor of pathology in the school of medicine, University of Rochester, has received the honorary degree of doctor of science from Colgate University.

Carl Ten Broeck, professor of bacteriology in the Peking Union Medical College, has been appointed a member of the Rockefeller Institute for Medical Research.

William B. Wherry, professor of bacteriology in the University of Cincinnati, has led a commission to Mexico to study the treatment of typhoid fever.

Joseph C. Springer, for many years coroner's physician in Chicago, has been appointed criminologist, a newly created position sponsored jointly by the chief of police of Chicago and the coroner of Cook County.

Warren C. Hunter has resumed his work in pathology at the University of Oregon Medical School after completing his term as medical fellow of the National Research Council.

Louis C. Punch has been appointed associate in pathology in the Medical College of Virginia at Richmond.

William H. Welch, professor of history of medicine at the Johns Hopkins Medical School, has been awarded a Kober medal for research in scientific medicine by the Association of American Physicians.

Survey of Epidemic Encephalitis.—J. Pierpont Morgan and William H. Mattieson have provided funds for a world survey of epidemic encephalitis, under a commission consisting of Haven Emerson, Frederick P. Gay, William H. Park and Josephine B. Neal, all of New York.

Prize for Treatment of Leukemia.—A philanthropist in Holland offers a prize of $50,000 for the best work on the treatment of leukemia. Contestants should send their reports to Prof. Hymans Van den Berg, Medical Clinic, Utrecht, Netherlands, before March 1, 1928. In case a member of the donor's family, suffering from myeloid leukemia, shall be cured by the method prescribed in the prize work, the amount of the prize will be doubled.

Death of Author of "The Microtomist's Vade-Mecum."—Arthur Bolles Lee, 1849-1927, the author of "The Microtomist's Vade-Mecum," which has appeared in seven editions, the first in 1885, and which has been of great service to Microtomists everywhere, died recently in Switzerland where he spent almost all of his life.

Marchiafava Prize.—The prize of the Marchiafava Foundation for the best work on pathogenic anatomy and experimental pathology has been awarded to Ugo Soli, professor of pathologic anatomy at Palermo, for his researches in experimental arteriosclerosis from *Spiroptera sanguinolenta* and to Raffaele Brancati, professor of surgery in Rome, for his investigations on internal experimental tar cancer.

International Society for Microbiology.—A society with this name was organized in Paris last April during the international conference on hydrophobia. The president is J. Bordet of Brussels and the general secretary is R. Kraus of Vienna. The first congress will be held in Paris in October, 1928.

The Osiris Science Prize.—This prize, which consists of $4,000, has been awarded to Charles Nicolle, director of the Pasteur Institute in Tunis, for his work on typhus fever and other infectious diseases.

Abstracts from Current Literature

Pathologic Physiology

Intradermal Salt Solution Test in Scarlet Fever. Beatrice R. Lovett, Am. J. M. Sc. **173**:539, 1927.

The time required for disappearance of the wheal made by injecting 0.2 cc. of 0.8 per cent sodium chloride solution, intradermally, was found to be shortened in scarlet fever, and roughly so in proportion to the severity of the disease. In the absence of complications, the time returned to normal rapidly, usually before the patient was ready to be out of bed. Urticaria was associated with shortened time of disappearance. In the early stages of the attack marked shortening of the time for the disappearance of the wheal is an indication for giving antitoxin.

Transplantation and Individuality Differential in Strains of Inbred Rats. Leo Loeb and Helen Dean King, Am. J. Path. **3**:143, 1927

Inbreeding of rats through successive matings of brother and sister does not lead to distinct diminution of the reaction against transplants within the inbred families. The results with rats differ from those with guinea-pigs in which inbreeding reduces the intensity of the reaction to transplants.

An Investigation of the Effect of Long-Continued Ingestion of Zinc, in the Form of Zinc Oxide, by Cats and Dogs. K. R. Drinker, P. K. Thompson and M. Marsh, Am. J. Physiol. **80**:31, 1927.

Following the administration by mouth of quantities of zinc oxide ranging from 175 to 1,000 mg. daily for periods of from three to fifty-three weeks, evidences of intoxication or other disturbances were not found, either clinically or by laboratory examination. The only possible exception to this statement was the finding of pancreatic fibrosis in three of ten cats, after a dosage of zinc far in excess of any possible human exposure. It was found that a small part of the zinc was excreted in the urine, the greater part directly into the alimentary tract through the bile, and possibly through the pancreas. There was an increased concentration of zinc in the organs concerned in elimination, as well as in the bone and bone marrow. This fell toward the normal level when administration was discontinued.

H. E. Eggers.

The Effect of Zinc Administration Upon Reproduction and Growth in the Albino Rat. P. K. Thompson, M. Marsh and K. R. Drinker, Am. J. Physiol. **80**:65, 1927.

Albino rats were fed with solutions of organic zinc salts — acetate, citrate and malate, or with zinc oxide suspensions in doses of from 2 to 38 mg. of zinc daily for many weeks prior to mating, and during pregnancy and lactation, without any significant effect on health of parents, fertility, and health and growth of offspring, even when the latter in turn were subjected to the zinc feeding. In normal animals there was found to be a practically constant concentration of zinc at all ages — 0.038, 0.039, and 0.040 mg. of zinc per gram of tissue being found, respectively in new-born, 60 day old, and adult rats. The writers consider this as suggestive of some functional importance on the part of the metal.

H. E. Eggers.

STUDIES ON THE ANTERIOR LOBE OF THE PITUITARY BODY. W. S. JOHNS, T. O. O'MULVENNY, E. B. POTTS and N. B. LAUGHTON, Am. J. Physiol. **80**:100, 1927.

Injection of extracts of the anterior lobe of the pituitary body of the ox, into healthy adult dogs, caused hyperglycemia, polyuria and glycosuria. In dogs which had been previously treated with the extracts, polyuria and glycosuria followed renewed injection, but the hyperglycemia was lacking. The writers consider that the lack of hyperglycemia was due to increased hepatic glycogenolysis, while the continued glycosuria is the result of a lowered renal threshold value for dextrose. Action of the extract on blood pressure and uterine muscle strips was not similar to that of "pituitrin." Control injections of liver and muscle tissue into healthy dogs failed to give similar results.

H. E. EGGERS.

THE INDUCTION OF PRECOCIOUS SEXUAL MATURITY BY PITUITARY HOMEOTRANSPLANTS. P. E. SMITH, Am. J. Physiol. **80**:114, 1927.

Fragments of homoplastic pituitary gland were introduced daily into the muscles of the legs of young rats, with the effect of inducing sexual maturity in the female as early as the weaning date, 22 days of age. In animals in which the treatment was begun on the fourteenth day of age, sexual maturity was attained in from eight to ten days. If begun on the weaning date, five or six days was required. Pituitary ablation on the other hand was followed by delayed establishment of the vaginal canal, and a failure of the genital system to develop. Only the anterior portion was concerned here, the posterior lobe being without effect in this direction. In ovariectomized rats, the transplants did not stimulate development of uterus or vagina.

H. E. EGGERS.

SUSCEPTIBILITY OF ALBINO RATS TO TETANUS TOXIN FOLLOWING ADRENALECTOMY. J. M. ROGOFF and E. E. ECKER, Am. J. Physiol. **80**:200, 1927.

An investigation of the effect of tetanus toxin on albino rats which had been partially or wholly deprived of their suprarenals, failed to give any foundation for the belief that such procedure results in increased susceptibility.

H. E. EGGERS.

THE EFFECT OF THE EXPERIMENTAL ADMINISTRATION OF EXCESSIVE AMOUNTS OF WATER ON THE VOLUME AND CONCENTRATION OF THE BLOOD. C. H. GREENE and L. G. ROWNTREE, Am. J. Physiol. **80**:209, 1927.

Following the forced administration of excessive amounts of water to dogs, demonstrable changes in volume and concentration of the blood were observed. Plasma volume was increased; hemoglobin and serum proteins were reduced. Electrolytes were also reduced, disproportionately in the case of sodium and chlorides. The urea and sugar content were largely determined by other factors than that of dilution, and so were partially independent of the administration of water.

H. E. EGGERS.

ALTERATIONS IN THE PERMEABILITY OF SKIN CAPILLARIES DURING PREGNANCY AND PUERPERIUM. W. F. PETERSEN and A. F. LASH, Arch. Int. Med. **39**:12, 1927.

The permeability index is determined by applying a cantharides plaster on the forearm for six hours; the plaster is then removed and the area is care-

fully watched for the first sign of blister formation. This is taken as the blister time. The blister fluid and blood serum were examined for protein by the refractometer. The ratio $\frac{\text{blister protein}}{\text{serum protein}}$ is used as the permeability index. The inflammatory response of the skin and capillaries called the inflammatory index is determined by the $\frac{\text{permeability index}}{\text{time of blister formation}}$. The capillary permeability of the skin during pregnancy averages 70.5 per cent (forty-seven cases). During labor the permeability is reduced and the blister time increased (sympathetic tonus of the skin). During the puerperium the average permeability is 73.6 per cent (fifty-five cases). Psychosis, hematemesis, threatened abortion, postpartum eclampsia and sepsis were associated with increased permeability. Hypertension and nephritis were either high or low in capillary permeability, except in one case.

S. A. LEVINSON.

THE PERMEABILITY OF THE SKIN CAPILLARIES IN VARIOUS CLINICAL CONDITIONS. W. F. PETERSEN, Arch. Int. Med. **39**:19, 1927.

Capillary permeability of the skin and the relative autonomic tonus of the arterioles has been studied by means of the cantharides blister. Maximum permeability and parasympathetic tonus are found in generalized dermatitis. Decompensation is associated with increased permeability. When due to renal or arteriosclerotic changes, the skin tonus may remain sympathetic. Glomerulonephritis is associated with increased permeability with sympathetic arteriole tonus. Chronic nephritis (arteriosclerotic) is associated with diminished capillary permeability and sympathetic arteriole tonus. Acute infections show increased permeability with normal or increased sympathetic tonus. The increase in permeability persists immediately after defervescence. Chronic tuberculosis shows normal or diminished permeability with normal or increased sympathetic tonus; advancing tuberculosis, an increase in permeability. Improvement is coincident with a diminution of capillary permeability. Ulcer of the stomach and intestine shows a relatively high permeability; carcinoma, a somewhat lower range. This may be due to differences in the age groups. Exophthalmic goiter has a distinct parasympathetic arteriole tonus but the permeability may vary from high to low. The cases with low permeability are usually those with a high blood pressure. The degree of permeability bears no relation to the basal metabolic rate. Paget's disease of the bones and arthritis deformans have an increase in permeability. The same holds true for postencephalitic parkinsonian syndromes and for obesity. Following surgical operations the permeability is increased and a similar condition is found in ophthalmologic cases, with or without operation. This may be due to the anesthesia, to the resorption of necrotic material, or to reflex effects from the pain associated with these conditions.

S. A. LEVINSON.

THE DETOXICATION OF PUTREFACTIVE PRODUCTS BY THE HUMAN BODY. F. W. POWER and C. P. SHERWIN, Arch. Int. Med. **39**:60, 1927.

There are two general classes of the products of decomposition formed from protein in the lower intestine due to bacterial action, namely, the non-nitrogenous and the nitrogenous, or amino derivatives. The authors prepared the principal non-nitrogenous putrefactive products of the three amino-acids, phenylalanine, tyrosine and trypophane, namely, benzoic acid, phenylacetic acid, phenylpropionic acid, parahydroxybenzoic acid, parahydroxyphenylacetic acid, parahydroxyphenylpropionic acid, indolformic acid and indolacetic acid. These non-nitrogenous putrefactive products were fed to human beings in order

to determine their toxicity; then the urine was examined in order to identify the product of detoxication and hence the method of detoxication by the body. Phenylpropionic acid was oxidized to benzoic acid, which was then combined with glycocoll and excreted as hippuric acid. Phenylacetic acid was excreted in combination with glutamine. The other acids were excreted uncombined. Of the nitrogenous or amino derivatives of the foregoing amino-acids, namely, phenylethylamine, tyramine and indolethylamine, all three were prepared and fed in amounts of 1 Gm. during a period of twenty-four hours. These amino compounds proved much more toxic than the non-nitrogenous substances. They were detoxicated by the body by splitting off the nitrogen, thus converting them into the acidic compounds of the type mentioned. The site of these detoxication reactions would appear to be chiefly the liver, but to some extent this function may be performed by the kidney or the gastro-intestinal wall. The authors are of the opinion that the human body is apparently provided with a chemical defense mechanism, nonspecific in character, which is more than adequate for the detoxication of the small amount of putrefactive products normally produced in the human intestine by the action of putrefactive bacteria on unabsorbed protein material.

S. A. Levinson.

The Mechanism of Pain in Gastric and in Duodenal Ulcer. W. L. Palmer, Arch. Int. Med. **39**:109, 1927.

Palmer believes that the pain producing mechanism is directly associated with the ulcer and does not depend on gastric or duodenal tone, or motility or pylorospasm. Under certain conditions, normal gastric peristalsis may constitute an adequate stimulus to the pain-producing mechanism. Evidence is presented to show that hydrochloric acid may sensitize both sensory and motor mechanisms. Under certain conditions, the pain of gastric carcinoma can be initiated by the introduction of 1.5 per cent hydrochloric acid solution into the stomach, and be relieved by its withdrawal or neutralization. Muscle tension is at times a factor in the pain of carcinoma. A third type of pain is apparently due to carcinomatous infiltration of the fibers of the sensory nerve. Antacid therapy will completely relieve the pain due to acid irritation, and in some instances give complete relief from the pain of carcinoma. Antacid therapy may desensitize the pain-producing mechanism so that it is no longer sensitive to 1.5 per cent hydrochloric acid solution.

S. A. Levinson.

Vitamin E and Iron Assimilation. Nina Simmonds, J. E. Becker and E. V. McCollum, J. A. M. A. **88**:1047, 1927.

Vitamin E is associated with iron assimilation functionally. The death of fetuses in rats on diet deficient in this vitamin is due to a crisis in iron assimilation which can be obviated by providing vitamin E in proper amounts from the beginning of pregnancy. Ferric salts are a better source of iron for growing rats than ferrous salts. Liver fats contain vitamin E in considerable amounts and liver contains iron, and the special value of liver diet lies in these facts. The results appear to provide new points of view with respect to faulty nutrition as causing sterility and pernicious anemia.

The Nature of Shock Symtoms Occasionally Following Drugs or Vaccines. E. F. Müller, C. N. Myers and W. F. Petersen, J. A. M. A. **88**:1128, 1927.

Evidence has been found that the clinical symptoms of sudden attacks, such as those designated "nitritoid crisis," occasionally following the intravenous

injection of arsphenamine and other drugs or serums, are caused by a sudden reaction of the entire vascular system as well as of almost all organs in the body. This reaction is largely the same as a reaction following the injection of living organisms (chill, etc.). Chills and nitritoid crises do not occur before the foreign bodies (drugs, bacterial toxins, proteins) have been deposited in the tissues. Therefore, drugs like arsphenamine, which disappear from the circulation almost instantaneously, give an early opportunity for general reaction, which in the case of bacterial invasion cannot occur before they are dissolved and their toxins are distributed. Such a general reaction consists of a more or less intensive contraction of the peripheral vessels with simultaneously decreased activities of the peripheral organs, skin and muscles. At the same time, an equally intensive vasodilatation takes place in the splanchnic region connected with an increase in the functional activities of the splanchnic organs (increased production of lymph, or stomach juice, acid, etc.). The latter frequently is associated with nausea and vomiting.

This entire reaction, differing in the two groups of organs, is connected with definite changes in the distribution of leukocytes. It is not known whether a special center in the brain is responsible for that reaction.

The systemic reaction designated as "nitritoid crises," and manifested by definite vasomotor phenomena in all organs involved, is obviously a reaction of the vegetative nervous system. It depends in its clinical intensity merely on an exaggeration of biologic reactions normally manifest in every individual after the administration of arsphenamine, vaccines, serums and proteins.

AUTHORS' SUMMARY.

PHYSIOLOGICAL EFFECTS OF DIETS UNUSUALLY RICH IN PROTEIN OR INORGANIC SALTS. T. B. OSBORNE, L. B. MENDEL, E. A. PARK and M. C. WINTERNITZ, J. Biol. Chem. **71**:317, 1927.

The blood of rats on a protein-rich diet has a somewhat higher content of nonprotein nitrogen than is normal. The kidneys become hypertrophied but the urine shows no abnormalities indicative of chronic renal disorders attributable to the protein. The feeding of urea in amounts equivalent to that derived from effective quantities of protein fails to bring about an equally noticeable renal enlargement.

ARTHUR LOCKE.

COD LIVER OIL CONCENTRATE. ITS VALUE AS AN ANTIRACHITIC AGENT WHEN INJECTED SUBCUTANEOUSLY. B. KRAMER, S. D. KRAMER, D. H. SHELLING and M. J. SHEAR, J. Biol. Chem. **71**:699, 1927.

A cholesterol-free concentrate prepared by the method described was found to be as potent as cod liver oil itself in amounts equivalent to the original oil. The concentrate, when injected subcutaneously in an ether solution, cured rats of experimental rickets. The same concentrate is inactive when injected subcutaneously with palmitin as the solvent.

AUTHORS' SUMMARY.

BLOOD FIBRIN AND EXCRETION OF NITROGEN IN OBSTRUCTION OF UPPER GASTRO-INTESTINAL TRACT. RUSSELL L. HADEN and THOMAS G. ORR, J. Exper. Med. **45**:433, 1927.

Blood fibrin increases rapidly after obstruction of the intestinal tract high up. The increase parallels the toxemia. The results indicate that the hepatic insufficiency is not the cause of death from such obstruction. After obstruction of the cardiac end of the stomach and after obstruction and release of the

pylorus, there is an increase in the excretion of nonprotein nitrogen, due to accelerated protein destruction or to the action of some toxic body.

COLLECTION OF ENTIRE EXTERNAL SECRETION OF THE PANCREAS UNDER STERILE CONDITIONS AND THE FATAL EFFECT OF TOTAL LOSS OF PANCREATIC JUICE. ROBERT ELMAN and JOHN M. MCCAUGHAN, J. Exper. Med. **44**:561, 1927.

By intubation of the main pancreatic duct in the dog, all the external secretion of the pancreas can be collected under sterile conditions. Under these circumstances death occurs in a characteristic way in about one week with anorexia, gastric irritability, vomiting and asthenia.

THE SUPPOSED PRESENCE OF A PRESSOR SUBSTANCE IN THE BLOOD OF PATIENTS WITH HIGH BLOOD-PRESSURE. F. R. CURTIS, A. A. MONCRIEFF and S. WRIGHT, J. Path. & Bact. **30**:55, 1927.

The authors attempted to check the recent claims of Danzer, Brody and Miles that striking pressor effects are obtained by injecting unchanged blood of patients with hypertension into animals. Cats were anesthetized with ether and then with chloralose intravenously. Heparin was employed to prevent coagulation of the blood. The animals were desensitized to human blood, after which 10 cc. of blood obtained from patients with hypertension was injected intravenously. No evidence was obtained of the presence of a pressor substance in the blood of patients with hypertension.

E. M. HALL.

KIRCHHEIMER FAMILIES OF BLEEDERS. W. J. KLUG, Deutsche Ztschr. f. Chir. **199**:145, 1926.

Of fifty-two families descended from the Mampel bleeder family, hemophilia is found in only twelve. Klug makes some corrections in Lossen's figures. He finds only one true bleeder marriage (marriage between bleeder and transmitter). In the hundred years during which this family has been known in the medical literature, the disease has never appeared in females or been transmitted by males or from grandmother directly to grandson. In regard to transmission by males, Klug remarks that most of the bleeders have died too young to have progeny. His statistics show, in the males, twenty-seven bleeders, thirty-nine nonbleeders; in the fifty-eight females, fourteen transmitters and ten nontransmitters, the rest of the female members of the bleeder branches of this family either died young or are childless up to the present time. The presence of nontransmitting females in this family goes far to prove the validity of Bauer's application of Mendel's law to hemophilia.

SIGNIFICANCE OF EXPERIMENTAL COOLING OF THE BODY WITH REFERENCE TO COLDS. LUDWIG FLEISCHER, Ztschr. f. Hyg. u. Infectionskrankh. **107**:2, 1927. BACHMANN and LUDWIG FLEISCHER, ibid., p. 28.

The author reports on a large series of experiments on himself concerning the relations between skin temperature and warmth of the surrounding atmosphere. At the same time he carefully observed his general condition during the course of the experiments. These observations were made while he was sitting quietly, either in his ordinary clothes, in light clothes or without clothes. He measured the temperature of the skin over the extensor surface of the basal phalanx of the left middle finger and of that over the third intercostal space close to the sternum. A third measurement which he considers to be particularly important is that of the temperature between fingers because it

gives some indication of the temperature of the deeper tissues. As long as the finger temperature did not decrease below 30 C. he did not notice any general effects except perhaps a slight feeling of coolness. In ordinary clothes the surrounding temperature in the absence of any drafts was indifferent between 18.5 and 21 C. In the afternoon both limits were lower. When the finger temperature rose above 33 C. he felt too warm. When the finger temperature dropped to 25 C. his hands felt cold. When it fell below 21 C. he began to feel cold generally. If at this point the experiment was interrupted the finger temperature under favorable conditions rose to 30 C. and his feeling of well being was completely restored. If the finger temperature had gone down below 20 C., general disturbances continued for the rest of the day such as: backache, coldness of the back, drowsiness and marked depression. At a finger temperature of 8.5 C., cramps developed in the muscles of the hands. In ordinary clothes and with an indifferent temperature in the surroundings the temperature between fingers was from 1 to 1.5 C. higher than the finger temperature. When the finger temperature decreased the difference between the two temperatures decreases until they were almost equal. The skin reacted in the same manner during a period of 6 months. It did not become more resistant to cooling but the sensitiveness to cold was somewhat reduced. The influence of hot drinks and of alcohol on the experimental results was interesting. From 15 to 25 cc. of alcohol in the form of alcoholic liquor or diluted absolute alcohol of approximately room temperature produced a strong subjective sense of warmth, raised the finger temperature but not that of the skin over the chest, whereas hot alcoholic and nonalcoholic drinks of a temperature of about 60 C. in quantities of about 300 cc. had exactly the same effect on the temperature of the fingers and also raised the temperature of the skin of the trunk. Hot nonalcoholic drinks were more valuable to correct the ill effects produced by cooling; they also prevented them to some extent when taken before the experiment was started. Hot water had the same effect as coffee or tea.

The observations which Fleischer had made on himself in regard to the relation of the temperature of the skin of the fingers to the general effects of exposure to cold were confirmed on other persons, also that hot drinks counteracted the effects of exposure, while the taking of cold alcoholic beverages was not equally efficacious. Neither one of the authors contracted cold during these experiments, although both were susceptible to cold as shown by the fact that during the period of experimentation they contracted colds in other ways. Observations on other persons, however, seemed to indicate that an acute attack of cold may follow a sudden reduction of body temperature by a cold wind or rain. Colds contracted in this way apparently are not infectious.

W. Ophüls.

Pathologic Anatomy

Hemihypertrophy and Twinning. Arnold Gesell, Am. J. M. Sc. **173**:542, 1927.

In 1921, the author reported a case of hemihypertrophy with bibliography (*Arch. Neurol. & Psychiat.* **6**:400 1921). He now reports a second case. Both the patients are mentally defective. Reexaminations indicate that physical and mental features remain relatively constant. There are now fifty-three recorded cases altogether; twenty-three were in males and thirty in females; the right side was affected in thirty-five and the left in eighteen; skin complications were present in twenty-four and mental subnormality in

eight. Hemihypertrophy is interpreted as a minimal form of twinning. The relatively high incidence of mental defect probably would have been found still higher if more and careful examinations had been made. The mental defect is ascribed to disturbance of normal development connected with twinning. A supplementary bibliography is given.

METASTATIC OR EMBOLIC ENDOMETRIOSIS, DUE TO MENSTRUAL DISSEMINATION OF ENDOMETRIAL TISSUE INTO THE VENOUS CIRCULATION. JOHN A. SAMPSON, Am. J. Path. **3**:93, 1927.

The conclusions of this profusely illustrated article are: Fragments of endometrial tissue at times are disseminated into the venous circulation during menstruation, from the mucosa lining the uterine cavity and also from ectopic endometrial foci; metastatic or embolic endometriosis arises from the implantation of these emboli in nearby veins. Endometrial tissue set free by menstruation, therefore, is sometimes not only alive but may actually continue to grow if transferred to situations favorable to its existence.

THE FINER VASCULAR CHANNELS OF THE SPLEEN. WARD J. MACNEAL, SADAO OTANI and MARJORIE B. PATTERSON, Am. J. Path. **3**:111, 1927.

A special technic for studying the human spleen is proposed. "The blood circulation in the spleen is essentially an open circulation in that the pulp spaces constitute the connecting channels through which the blood passes from arterial capillary to venous sinus." The article is illustrated by eight plates, three of which are in colors.

ISLANDS OF LANGERHANS IN HUMAN PANCREAS. SADAO OTANI, Am. J. Path. **3**:123, 1927.

In hypertrophy of the islands in the adult, there is transformation of acinar and centro-acinar cells. The acinar cells can change into island cells. Most of the islands are connected with acini, and new islands may form from acinar, centro-acinar or duct cells.

TWO CASES OF ESSENTIAL ADRENAL INSUFFICIENCY (ADDISON'S DISEASE). G. M. MEDLAR, Am. J. Path. **3**:135, 1927.

In both cases there was atrophy and ptosis of the suprarenals with status lymphaticus. It is suggested that status lymphaticus is the expression of an attempt to overcome a deranged metabolism due to lack of suprarenal secretion.

THE OCCURRENCE OF PARATHYROIDS ON THE ANTERIOR SURFACE OF THE THYROID GLAND [IN MAN]. R. J. MILLZNER, J. A. M. A. **88**:1053, 1927.

Parathyroids may occur on the anterior surface of the thyroid in a large percentage of persons, and it is recommended in thyroidectomy to leave behind the lateral and anterior parts of the thyroid capsule.

SPRAIN OF CERVICAL SPINE CAUSING THROMBOSIS OF ANTERIOR SPINAL ARTERY. ROY R. GRINKER and CHESTER C. GUY, J. A. M. A. **88**:1140, 1927.

In a case of "spinal sprain" in the region of the fifth cervical vertebra with resulting thrombosis of a portion of the anterior spinal artery, the subsequent cord softening affected the central and anterior gray matter, extending peripherally to involve completely the crossed pyramidal and spinothalamic tracts and the bases of the medial portion of the posterior columns.

After mild trauma or muscular exertion, evidence of cord lesion without fracture or dislocation may be due to temporary vertebral luxation.

AUTHORS' SUMMARY.

TRANSPLANTATION OF GUINEA-PIG SUPRARENAL. HENRY L. JAFFE, J. Exper. Med. **45**:587, 1927.

Autoplastic transplants of suprarenal cortex in the abdominal wall may remain for months and may grow so that life may be maintained after complete suprarenalectomy, but homoplastic transplants usually degenerate.

EXPERIMENTAL ATHEROSCLEROSIS IN RABBITS. SHEPARD SHAPIRO, J. Exper. Med. **45**:595, 1927.

Alimentary hypercholesterolemia in rabbits for 110 days or longer causes deposition of cholesterol in the intima of the aorta. Removal of the thyroid, spleen and gonads hastens the development of atheroma in hypercholesterolemia, but suprarenal insufficiency has no such effect.

RELATION OF THE RETICULO-ENDOTHELIAL SYSTEM TO AMYLOID FORMATION. H. SMETANA, J. Exper. Med. **45**:619, 1927.

The following points favor the view that reticulo-endothelial cells are concerned in the formation of amyloid: amyloid appears where the cells are normally present, in small patches, and in close relation to the cells; in the liver, amyloid may appear in patches apparently within the capillaries and after blocking the reticulo-endothelial cells with India ink, there is delay in the appearance of amyloid in mice given nutrose subcutaneously.

XANTHOMA. M. LOUSTE, Paris méd. **63**:64, 1927.

The lesion is formed of large connective tissue cells, xanthoma cells, containing fatty granules. The latter represent neutral fats, or glycerol ester, and lipoids, or cholesterol ester. Fatty acids in excess in the blood are retained in these cells and oxidized. The rôle in the phenomenon of amboceptor cells or Langerhans' cells is explained. Thus hypercholesterolemia is a factor in the formation of xanthoma.

CHRONIC BRONCHOPNEUMONIA WITH GIANT CELLS AND CUBICAL ALVEOLAR EPITHELIUM. J. ZEYLAND, Trav. des Instituts de Anat. Path. des Universités de Pologne **2**:34, 1927.

The formation of giant cells and cubical alveolar epithelium in chronic bronchopneumonia need not be a so-called specific process. The process may occur in measles, whooping cough, diphtheria and other conditions. Three instances are described in infants.

THE TRACHEA IN GOITER. HELENE SCHUSTER, Trav. des Instituts d'Anat. Path. des Universités de Pologne **2**:79, 1927.

A case of death from hemorrhage on removal of a cannula after tracheotomy on account of dyspnea from the pressure of a large goiter in a girl, aged 18, is described. The hemorrhage resulted from erosion by pressure from the cannula on the arteria anonyma. Following compression by goiter, there may be thinning of the tracheal wall, especially in the young. Special precautions should be taken to prevent injury to the trachea by the cannula in such cases.

LIPOMA OF GALLBLADDER. MARIE ZELEWSKA, Trav. des Instituts d'Anat. Path. des Universités de Pologne **2**:96, 1927.

The tumor arose from the fundus of the bladder; it had a diameter of 3 cm. and occurred in an old woman without a tendency to adiposity.

ALTERATIONS OF THE SKULL IN EPILEPSY AND IDIOCY WITH CONSIDERATION OF THE OSSIFICATION OF THE SUTURES. Marterna, Verhandl. d. Deutsch. path. Gesellsch. **21**:333, 1926.

Alterations of the skull are frequently found in idiocy and epilepsy. They were observed in 40 per cent of the epileptic patients and 60 per cent of idiots after exclusion of the alterations which appeared after the cessation of bony growth. The premature synostoses of the sutures were the most frequent alteration in epileptic patients, while microcephalic patients had the first place in idiots. Partial premature ossifications of the sutures were present in 22 per cent of the epileptic patients and in 19 per cent of the idiots. These synostoses did not interfere with the growth of the skull in the direction vertical to that of the synostosis. Many of the synostoses were interpreted as the result of a primary trauma of the brain, but there were also cases in which the synostoses were the primary alterations and possibly the cause of the epilepsy (primary synostotic epilepsy).

WILHELM HUEPER.

IMPORTANT GENERAL FEATURES OF EXPERIMENTAL TUBERCULOSIS IN GUINEA-PIGS. PAGEL, Verhandl. d. deutsch. path. Gesellsch. **21**:347, 1926.

After injection of gold preparations the normal resistance of the kidney of guinea-pigs against tuberculous infection breaks down and epithelioid tubercles appear in the space of Bowman's capsule, while the necrotic processes which are marked in the kidneys of normal animals after injections of gold preparations are of a minor degree. The vascular alterations of tuberculous guinea-pigs involving usually the postcapillary veins of the lung are classified in two main groups, those with a specific tuberculous structure and those without. Different types in the first group are the tuberculous periphlebitis and endophlebitis which latter is divided into miliary tubercle, polypous endangitis and tuberculous thrombophlebitis. Fungoid nodules of the intima containing granulocytes are present in the vascular changes of the second group. These endothelial granulomas are interpreted as nonspecific reactions of the vascular wall against the attack of the tubercle bacilli. Another nonspecific reactions is the appearance of granulocytic and hemopoietic transformations of endothelial cells of capillaries of various organs. The course of the primary infection of the lung is similar to that of the human lung.

WILHELM HUEPER.

THE BEGINNING AND FREQUENCY OF THE ATHEROSCLEROSIS. S. SALTYKOW, Verhandl. d. deutsch. path. Gesellsch. **21**:398, 1926.

The yellow spots in the intima of the aorta of children represent the first signs of atherosclerosis and usually develop later into extensive atherosclerotic alterations. Lipoid deposits as well as proliferations of the intima are characteristics of atherosclerosis and may occur independently of each other. Atherosclerotic changes are found in children a few months old and are present in all persons after the eighth year. Among the infectious diseases, tuberculosis possesses a special significance in regard to the etiology of atherosclerosis.

WILHELM HUEPER.

PHLEBITIS TYPHOSA. W. Ceelen, Verhandl. d. deutsch. path. Gesellsch. **21**:415, 1926.

Button-like, polypous, flat formations of typhoid granulation tissue were observed in the wall of veins of the spleen, intestine and mesenteric lymph nodes. They were either the result of an endophlebitis or of a periphlebitis. In the latter case the granulation tissue penetrating the vascular wall projected into the lumen but remained covered with endothelium. Thromboses with secondary necroses (spleen, intestine) may result.

WILHELM HUEPER.

THE MECHANISM OF THE HEMORRHAGIC MENINGITIS IN ANTHRAX INFECTION. STEPHAN BÉZI, Verhandl. d. deutsch. path. Gesellsch. **21**:435, 1926.

Hemorrhages in the meninges or brain are present in 40 per cent of fatal infections with anthrax and are sometimes the cause of death. The anthrax bacilli lodge in the arachnoid and proliferate in the meningeal fluid when they have disappeared from the blood on account of the bactericidal action of the serum. They produce necrosis of the wall of the small and median sized vessels, resulting in rupture and hemorrhage.

WILHELM HUEPER.

SPECIFICITY OF LIPOID STAINING REACTIONS. C. KAUFMANN and E. LEHMANN, Virchows Arch. f. path. Anat. **261**:623, 1926.

In an attempt to determine the specificity of the staining reactions of lipoids, the sudan, Nile blue, Fischler, Smith-Deitrich and Schulze reactions were applied to fat-free vegetable pith which had been saturated in vacuo with known saturated and unsaturated fatty acids, neutral fats, triglycerides and natural fats, cholesterol, lecithin, and mixtures of these various substances. Sudan III was found to stain all of the fatty acids, fats and fat mixtures except palmitic and stearic acid and is considered the most useful of the various methods tried. No method is specific for any single lipoid substance or even for any group of such substances.

O. T. SCHULTZ.

SIMILARITY OF TISSUE CHANGES IN CHRONIC HYDROCYANIC ACID POISONING AND BERIBERI. N. MESSERLE, Virchows Arch. f. path. Anat. **262**:305, 1926.

Experimental intoxication of animals with hydrocyanic acid leads to decreased cellular oxidation and causes paralyses similar to those of experimental beriberi, in which Hess, Messerle and others had also described diminished tissue oxidation. In a comparative study of the tissue changes in pigeons with beriberi and with chronic hydrocyanic intoxication, Messerle found practically identical degenerative changes in the voluntary musculature, peripheral nerves and spinal cord. Hypertrophy of the suprarenals, described as a usual condition in beriberi, was present also, but in less marked degree, in pigeons intoxicated with hydrocyanic acid.

O. T. SCHULTZ.

SPONTANEOUS RUPTURE OF THE SPLEEN. A. KROKIEWICZ, Virchows Arch. f. path. Anat. **262**:328, 1926.

In a man, aged 54, with symptoms of septic endocarditis, fatal collapse occurred suddenly while the patient was at stool. At necropsy, the peritoneal cavity was found filled with blood which had come from a rupture of the greatly enlarged spleen. The latter contained numerous infarcts; rupture had not occurred in any of these, but between them. The primary lesion was a vegetative, ulcerative aortic endocarditis.

O. T. SCHULTZ.

DIFFUSE SCLEROSIS OF THE SKIN. J. HEINE, Virchows Arch. f. path. Anat. **262**:351, 1926.

In a woman, aged 71, the skin became diffusely thickened and deeply pigmented, the process having lasted a year and a half. The thickened skin of the arms and legs pitted on pressure. Upon microscopic examination the epidermis was slightly atrophic, the cutis was moderately thickened and contained a few spindle nuclei, the subcutis was greatly thickened and densely fibrous, and the subcutaneous fat was atrophic. Diffuse interstitial fibrosis with atrophy of the parenchyma was present in the pancreas, thyroid and hypophysis. The thyroid and suprarenals were infiltrated by lymphocytes. The author is convinced that the condition described by him has nothing in common with scleredema, and differentiates it from scleroderma because of the diffuseness of the process in his case and the absence of any areas of origin from which the process spread. He considers his case a disease sui generis. Although the author believes that the condition described by him is not scleroderma, the fibrotic changes described by him in the endocrine organs are apparently identical with those described a number of years ago by Hektoen, and since seen so repeatedly by others as to suggest an endocrine origin for scleroderma.

O. T. SCHULTZ.

OSTITIS FIBROSA. F. J. LANG and K. HÄUPL, Virchows. Arch. f. path. Anat. **262**:383, 1926.

In previous publications Lang has taken a stand in opposition to that of most observers, that ostitis fibrosa is a characteristic bone disease of special type. He has held to the older view of von Recklinghausen that ostitis fibrosa is a process that is secondary to a variety of factors. Lang and Häupl present the results of a histologic study of five cases of localized ostitis fibrosa and three cases of the generalized form of the disease, two of the latter being associated with osteomalacia and one with rickets. In the localized cases, the fibrotic process was associated with a hemorrhagic cyst in one, with hemorrhage into the vertebrae in two cases of carcinosis of bone, with Kohler's disease of the second metatarsal in one, and with deforming arthritis of the second metatarsal in the fifth case. In such cases, the replacement of the fatty marrow by a loose, often mucoid, fairly well vascularized connective tissue, which process is combined with absorption of bone and with some new formation of bone, is held to be secondary to the disturbance produced in the bone by hemorrhage, trauma or other factors. In the generalized form, the process is likewise a reactive one, which is secondary to mechanical factors acting on bones that have been weakened by partial loss of their calcium content, as in osteomalacia, or by deficient calcification, as in rickets.

O. T. SCHULTZ.

FIBRINOUS RIDGES IN ACUTE PLEURITIS. A. LAUCHE, Virchows Arch. f. path. Anat. **262**:406, 1926.

Lauche claims that on the surface of the acutely inflamed pleura he has frequently seen regularly arranged ridges and networks of fibrin, such as are characteristic of acute pericarditis but have not received mention in pleuritis. The parallel ridges, which are often united into a network by finer cross ridges, usually occupy an area from 2 to 3 cm. wide and extending from apex to base over the posterior rounded border of the lung. In both the pericardium and pleura, the ridges are formed in a layer of deposited fibrin which cannot follow

the contraction and expansion of the underlying organ and in situations in which the amount of fluid exudate is great enough to prevent rubbing of the two serosal layers.

O. T. SCHULTZ.

GUMMA AND ANEURYSM OF THE LIVER. H. LENHARTZ and H. GÜRICH, Virchows Arch. f. path. Anat. **262**:416, 1926.

This is a clinical and anatomic report of an interesting case of gumma of the liver which had eroded a branch of the hepatic artery with the formation of a spurious aneurysm. In the terminal stages of the illness, the aneurysm perforated into the common duct, a process which was followed by the passage of large amounts of tarry blood in the stools and which led to the diagnosis of duodenal ulcer. Symptoms of acute cholecystitis and peritonitis led to laparotomy, at which the gallbladder was found distended with blood and perforated, and hemorrhagic exudate was present in the peritoneum. Cholecystectomy was followed by death. The antemortem clinical diagnosis was perforation of the gallbladder with biliary peritonitis. The exact conditions present were revealed only by the necropsy.

O. T. SCHULTZ.

CHANGES IN THE SOLAR PLEXUS FOLLOWING LAPAROTOMY. W. LEBEDENKO, Virchows Arch. f. Path. Anat. **262**:424, 1926.

The immediate postoperative period is characterized by a number of manifestations which the author interprets as evidence of involvement of the sympathetic nervous system. The effects on the celiac ganglia of abdominal operations were studied experimentally in dogs. To determine the effects of the individual procedures in such operations, well-fed and starved animals were killed after morphine narcosis, after combined morphine and ether or chloroform anesthesia, after anesthesia plus simple incision of the abdominal wall, and after anesthesia with laparotomy and handling of the intestines. Morphine alone caused only slight changes in the ganglion cells. The addition of chloroform or ether anesthesia caused partial disappearance of the tigroid substance. Laparotomy and handling of the abdominal organs resulted in still more marked cellular changes and in the degeneration of individual ganglion cells. Starvation intensified the alterations noted. Reparative changes were observed in ganglion cells when the animals were killed on the sixth or eighth day after operation. The tendency to gastro-intestinal and renal hemorrhages and to changes in the tonus of the gastro-intestinal tract, which may follow laparotomy in man, are interpreted as the result of changes brought about in the solar plexus by anesthesia and by the trauma of operation.

O. T. SCHULTZ.

PATHOGENESIS OF CYSTIC LIVER. L. WACKERLE, Virchows Arch. f. path. Anat. **262**:508, 1926.

In two still-born fetuses, a moderate grade of cystic liver was associated with cystic kidneys and other maldevelopments, and in a woman, aged 56, a more marked degree of formation of cysts in the liver was associated with bilateral cystic kidneys, which led to death in uremia. In the three livers, an excess formation of interlobular stroma had taken place, and at the periphery of the interlobular fields excessive numbers of small bile ducts lined by cuboidal epithelium were present. It was ducts of the latter groups which had become cystically dilated. The connection of peripheral interlobular ducts and cysts with intralobular bile canaliculi could be seen, but it was impossible to detect any communication of the cystic peripheral ducts with the main interlobular

ducts. Wackerle accepts the independent formation during embryonic development of the intralobular bile canaliculi and the extrahepatic duct system together with the interlobular ducts. The union of the two systems occurs in the peripheral one of the interlobular tissue, the smaller peripheral ducts in this zone in his cases belonging to the intralobular system. The process leading to cystic liver is looked on as a hamartoma, in the sense of Albrecht, which manifests itself by a disproportionate formation of interlobular mesenchymal tissue. The intralobular ducts are unable to penetrate this tissue, and hence fail to accomplish their union with the main interlobular ducts.

O. T. SCHULTZ.

CYSTIC MASTITIS IN THE EARLIER YEARS OF LIFE. E. HAHN, Virchows Arch. f. path. Anat. **262**:531, 1926.

In order to determine whether there is any relation between age and cystic disease of the mammary gland, Hahn made a microscopic study of breast tissue removed routinely at necropsy from forty-eight women between the ages of 14 and 40 years. The latter was taken as the upper age limit because Goens had previously reported a similar study based on material from sixty women over 40 years of age. In eleven of the forty-eight mammary glands studied, proliferation of the duct epithelium was evident and in five of this group this process was associated with cystic formation. Hahn believes that Reclus' or Schimmelbusch's disease is not inflammatory in origin, but that it begins as a primary proliferation of duct epithelium, which may already be manifest before the period of involution of the gland. The process occurs in a previously normal gland and bears no relation to misplacement. The epithelium of axillary apocrine sweat-gland type, which lines some of the ducts, has resulted from reversion of the proliferating duct epithelium. The fibrosis which may occur in Reclus' disease is not a primary phenomenon, but is the result of a stimulus exerted on the periductal tissue by the proliferating epithelium.

O. T. SCHULTZ.

AIR EMBOLISM IN CESAREAN SECTION. W. G. DEUCHER, Zentralbl. f. Gynäk. **50**:3025, 1926.

When the patient, apparently in good condition, was being removed from the operating table after transperitoneal cervical cesarean section, a severe hemorrhage from the vagina set in suddenly, respiration, hitherto quiet, became spasmodic, the patient became cyanotic and died. At necropsy, two and one-half hours after death, typical signs of air embolism were found. In view of the hemorrhage, it seems probable that uterine atony caused the empty veins of the floor of the placenta and perhaps of the cervical wound to gap and that moving the patient just at this time caused aspiration of air into a vein.

HETEROTOPE PROLIFERATION OF TISSUE RESEMBLING ENDOMETRIUM. CARL SEMB, Acta obstet. et gynec. Scandinav. **5**:200, 1926.

The author bases his conclusions on a study of seven cases of endometrial tissue in the ovary, one case of adenomyosis uteri externa, one of adenomyosis intestini tenuis, and one of adenomyosis ligamentum teres uteri. The age limits in his cases were from 25 to 50 years. The material studied consisted of parts removed at operation and sent to the laboratory for examination. In the ovary typical "tarry" cysts were found, with perforation in three patients. Adhesions about the ovaries were attributed to the irritating effects of the contents of the cyst.

In the ovary endometrium-lined cysts were found in contact with the lumen of follicular cysts, hence the author feels that the endometrial tissue in the ovary arises from follicular epithelium, or possibly is associated with epithelial defects in the ovary. To explain endometrioses in the serous layer of the uterus, small intestine and round ligament, the author tends to agree with De Jong that the different localizations can be traced to endometriogenic potentialities of the celomic epithelium. In his material, he states, there was no evidence in support of the theories generally advanced, in particular none in favor of Sampson's implantation theory which is not considered to fit in with the endometrial "tar cysts."

VICTOR JACOBSEN.

THE RELATION BETWEEN POLYCYTEMIA AND PORTAL THROMBOSIS. RUDOLF BRANDBERG, Acta. path. et microbiol. Scandinav. **3**:521, 1926.

There appears to be a close relationship between polycytemia and portal thrombosis. After reviewing the cases in the literature and describing a case of his own, Brandberg concludes that the portal thrombosis is secondary and due to the increased coagulability of the blood. In none of the cases were there any chronic changes in the portal vein or other local conditions that could account for the thrombosis.

TARTAR FORMATION. CARL NAESLUND, Acta. path. et microbiol. Scandinav. **3**: 627, 1926.

It appears that gingival calculi are formed chiefly by actinomyces and leptrothrix on which calcium salts are precipitated.

Pathologic Chemistry

THE AMYLASE-ACCELERATOR AND ANTI-TRYPSIN OF NORMAL HUMAN SERUM. CHARLES O'DONOVAN, JR., and WILBURT C. DAVISON, Bull. Johns Hopkins Hosp. **40**:238, 1927.

The blood serum of normal persons contains an amylase-accelerator and an antitrypsin, both of which are reduced about 50 per cent on heating the serum to 58 C. for thirty minutes.

THE EFFECT OF ACID AND BASE INGESTION ON THE ACID-BASE BALANCE. A. E. KOEHLER, J. Biol. Chem. **72**:99, 1927.

The p_H of the blood may be changed by several tenths in either direction from the normal and maintained for several weeks without disastrous effect. The ill effects of acidosis and alkalosis on the general well being and functional activity of the patient may be due to an associated depression of tissue oxidation.

ARTHUR LOCKE.

INTERRELATIONSHIPS BETWEEN THE CHEMICAL COMPOSITION OF THE BLOOD AND THE LYMPH OF THE DOG. R. M. ARNOLD and L. B. MENDEL, J. Biol. Chem. **72**:189, 1927.

The interchange of diffusible substance between the blood and lymph takes place with such ease that the two fluids do not differ greatly from one another in their composition, either under normal or abnormal conditions, except in protein content. The protein content of the lymph is approximately two-thirds that of the blood serum.

ARTHUR LOCKE.

STUDIES OF THE METABOLISM OF WOMEN: III. VARIATIONS IN THE LIPID CONTENT OF BLOOD IN RELATION TO THE MENSTRUAL CYCLE. R. OKEY and R. E. BOYDEN, J. Biol. Chem. **72**:261, 1927.

The blood lipid concentration of women undergoes a cyclic change which may coincide with the period of retrogression of the corpus luteum. The change consists of a decrease in the blood cholesterol concentration to about 70 per cent of the normal value and is usually immediately preceded or followed by a rise to about 124 per cent of the normal. The blood cholesterol concentration may also become reduced, intermenstrually, during slight, acute respiratory infections. There is no significant cyclic variation in the blood lecithin or fatty acid level.

ARTHUR LOCKE.

THE NORMAL EXCRETION OF ZINC IN THE URINE AND FECES OF MAN. K. R. DRINKER, J. W. FEHNEL and M. MARSH, J. Biol. Chem. **72**:375, 1927.

The zinc content of the foods which constitute an ordinary mixed diet is by no means negligible. Oysters, for instance, may contain as much as 0.23 per cent. The zinc content of a twenty-four hour collection of urine ranges, normally, from 0.25 to 2 mg., and of feces, from 2.67 to 19.9 mg.

ARTHUR LOCKE.

EXPERIMENTAL STUDIES ON HEMOGLOBIN RESISTANCE. GUNTHER BRANN and HANS BISCHOFF, Ztschr. f. Immunitätsforsch. u. exper. Therap. **49**:50, 1926.

The effects of sodium hydroxide on the hemoglobin resistance of young and old splenectomized and castrated rats were determined. The authors found that the hemoglobin of normal rats is more resistant to sodium hydroxide than that of man and that the hemoglobin of young rats is more resistant than that of old ones.

Splenectomy led to an increase in resistance which, however, came back to the normal in about three months. Castrated rats showed a lengthening of the testing time. Castration appeared to cause a diminution in size of the spleen, and the authors think that diminished activity of the spleen determines the increased resistance.

PAUL R. CANNON.

Microbiology and Parasitology

PNEUMONIA IN RABBITS. CARROLL G. BULL and G. HOWARD BAILEY, Am. J. Hyg. **7**:334, 1927.

The instillation of a weak solution of brilliant green into the nostrils of rabbits having *Bacterium lepisepticum* in the nasal passages gives rise to severe snuffles and thoracic infections which result in pneumonia, pleurisy and pericarditis. Similar infections can be readily induced in rabbts that are free of *Bacterium lepisepticum* by intranasal inoculation either before or after treatment with brilliant green.

AUTHORS' SUMMARY.

RESEARCHES ON HOOKWORM IN CHINA. W. W. CORT, J. B. GRANT, N. R. STOLL and other collaborators, Am. J. Hyg. **7**:398, 1928.

This report consists of a series of fifteen papers, embodying the results of the work of the China Hookworm Commission, which carried on its work from June, 1923, to November, 1924. The work of this commission was under the joint auspices of the department of pathology of the Peking Union Medical College and of the department of medical zoology of the School of Hygiene

and Public Health of Johns Hopkins University, and was financed by the International Health Board of the Rockefeller Foundation.

The investigations early crystallized into three general phases, with the following objects:

1. To add in every possible way to the knowledge of the distribution and importance of hookworm disease and infestation in China.

2. To study the epidemiology of the disease, as it occurs in China, with special reference to its spread by the use of night-soil for the fertilization of various crops.

3. To follow experimentally the life of hookworm eggs and larvae in night-soil in an attempt to discover methods by which this material can be used as fertilizer without spreading hookworm infestation.

Information was secured by the use of questionnaires and from a large series of dilution egg counts from different localities on the distribution of hookworm infestation and disease in China. Hookworm disease was found to be of no appreciable medical or public health significance in North China. In Central and South China hookworm infestation and disease have a wide distribution, but there are only a comparatively few areas in which this disease is one of the major public health problems, and its distribution is surprisingly localized.

A series of epidemiologic studies indicated that hookworm disease in China is a rural problem, and that its spread is chiefly due to the use of human excrement as a fertilizer. Its spread, however, was found not to be associated with the general use of human fertilizer, but with its use on specific crops in which the complicated series of conditions necessary for the development of the larvae and their entrance into the human host were realized.

In the cultivation of rice, the night-soil is placed on the fields under water with conditions such that any hookworm eggs present fail to develop and soon die. The conclusion was drawn that the cultivation of this crop not only does not spread hookworm infestation, but that the use of enormous quantities of night-soil on the rice field is an important control measure. Large areas devoted to cultivation of rice show almost no hookworm infestation.

The study of an area in which cotton was the chief crop showed only a light subclinical type of infestation and suggested that the cultivation of this crop is not an important source of hookworm disease.

Under ordinary conditions of fertilization, little hookworm was found to come from cultivation of vegetables, although when the night-soil was trenched or buried, considerable infection might be produced.

Of the types of crops studied, only the methods of cultivating the mulberry trees for the feeding of silkworms produced conditions favorable for the development of an important clinical hookworm disease in the population. This relation was due to the sequence of fertilizing the trees and picking the leaves, in which conditions were favorable for the development of the larvae in the soil and their entrance into the feet of the pickers. The evidence indicated that the cultivation of mulberry trees was related to the prevalence of hookworm disease over wide areas in the Yangtze Delta region, the Canton Delta and probably Szechwan province. There are centers where clinical hookworm disease has been reported outside the areas of silk production, but the evidence so far obtained points to the fertilization of mulberry trees as the outstanding factor in the production of clinical hookworm disease in China.

Experiments at Soochow and Canton on the viability of hookworm eggs in stored night-soil showed that over 95 per cent of the eggs were killed in about a month in the summer under the conditions of water storage. Less than two months produced a complete elimination of the ova. The admixture

of urine, refuse and certain chemical fertilizers hastened the process, and the introduction of lime in the ratio of from 1:10 to 1:500 to the total contents of the night-soil containers killed practically all the eggs in from six to twelve days.

In considering possibilities of control it is pointed out that there are apparently only a comparatively few regions in which the relative importance of hookworm disease would make an organized campaign feasible. In such regions, emphasis on storage of night-soil before use would seem to be the most important prophylactic measure. It is pointed out in conclusion that much further investigation will be necessary in numerous regions which were almost untouched in this survey, and on the relation of other crops than those studied, before an adequate picture of the hookworm situation in China can be obtained.

ETIOLOGY OF OROYA FEVER. HIDEYO NOGUCHI, J. Exper. Med. **45**:437, 1927.

Fatal infections with *Bartonella bacilliformis* in *Macacus rhesus* show the same changes that are found in persons who have died of Oroya fever: zonal necrosis about the hepatic veins and endothelial hyperplasia of the liver, spleen and lymphatic system. *Bartonella bacilliformis* was found microscopically and by cultures in tissues showing structural changes.

The cutaneous lesions known as verruga nodular, mular and miliar have been reproduced in monkeys.

INFLUENCE OF LIGHT ON THE REACTION TO INFECTION IN EXPERIMENTAL SYPHILIS. WADE H. BROWN and LOUISE PEARCE, J. Exper. Med. **45**:497, 1927.

In general the efficiency of the reaction increased with the amount of light received and with the constancy of exposure.

AN INFECTIOUS GRANULAR VAGINITIS OF COWS. F. S. JONES and RALPH B. LITTLE, J. Exper. Med. **45**:519, 1927.

A disease of cows beginning with acute vulvovaginitis is described. As the acute stage subsides the vaginal mucosa becomes studded with small red nodules consisting of densely packed lymphocytes in the submucosa. These nodules may persist for two or three months or longer. In the exudate was found a gram-negative bacillus from 1 to 2 microns in length, which stained with difficulty, and was provided with tiny polar granules. This bacillus was grown on slanted agar in sealed tubes with defibrinated horse blood, and the disease was reproduced in heifers or young calves.

SPREAD OF BACTERIUM LEPISEPTICUM INFECTIONS AT A RABBIT FARM. LESLIE T. WEBSTER, J. Exper. Med. **45**:529, 1927.

From 50 to 75 per cent of the total mortality on a rabbit farm, was due to *Bact. lepisepticum*. About 50 per cent of the stock had snuffles caused by the same organism. Both the mortality and snuffles showed spring and fall rises and low points in summer. Within each breed the infection varied, and individuals differed in their response. Some died from pneumonia and septicemia; some developed snuffles; some became carriers, and few remained unaffected.

SPONTANEOUS EPIDEMIC OF PNEUMONIA AND SNUFFLES IN RABBITS CAUSED BY BACTERIUM LEPISEPTICUM. DAVID T. SMITH, J. Exper. Med. **45**:553, 1927.

The epidemic, which was caused by mucoid strains, resulted from the introduction of virulent organisms among hitherto unexposed animals. Some died of pneumonia and septicemia, while others had only nasal infection, depending on degrees of resistance to the bacillus.

COMPARISON OF A VIRUS FROM EPIDEMIC ENCEPHALITIS (KOBAYASHI) WITH THE VIRUS OF RABIES. E. V. COWDRY, J. Exper. Med. **45**:799, 1927.

The virus obtained by Kobayashi from a case of epidemic encephalitis in Japan was found in animal experiments and cross-immunity tests to be indistinguishable from the virus of rabies.

DEGRADED PNEUMOCOCCI IN VIVO. H. A. REIMANN, J. Exper. Med. **45**:807, 1927.

No evidence was obtained from experiments that recovery from pneumoccus infection depends on the degradation of virulent S forms of pneumococci to virulent R forms.

RESISTANCE OF FOOT-AND-MOUTH VIRUS TO CHEMICALS. PETER K. OLITSKY and LOUIS BOËZ, J. Exper. Med. **45**:815, 1927.

The virus of foot-and-mouth disease exhibits a remarkable resistance to such bactericidal agents as the narcotic solvents (alcohol, ether, chloroform), or such antiseptics as phenol, bichloride of mercury, or cresol, as shown by tests made by others and ourselves. We have shown, however, that the resistance of the incitant to these chemicals is really masked. It is due to the fact that the reagents coagulate the proteins of the medium in which the virus is, as a rule, suspended. As a result, the active agent is protected by the coagula which prevents direct contact with the chemicals. On the other hand, if advantage is taken of the periodic phenomenon attending such processes, and coagulation is prevented, the virus can then be brought under direct action of the antiseptics. Under these conditions the incitant is more sensitive to destruction by the chemicals than is the living staphylococcus. As a corollary, the virus is destroyed as rapidly, or even more so, than are staphylococci by substances such as sodium hydrate (from 1 to 2 per cent solutions), or antiformin (1 per cent solution), which do not form coagula. We are therefore compelled to contradict the opinion that the extraordinary resistance to certain chemicals of the virus of foot-and-mouth disease, as it ordinarily occurs admixed with proteins, is an indication of its inanimate character.

The results of a large series of experiments lead to the conclusion that of a number of antiseptics employed the sodium hydrate in 1 to 2 per cent solutions is an effective virucide. It is capable of killing the virus within one minute, as shown by tests on cattle and guinea-pigs. Furthermore, its effectiveness is not diminished even when the virulent material is admixed with cattle's urine, with manure, or with garden soil. The experimental evidence and the cheapness suggest its use in field practice as a disinfectant.

AUTHORS' SUMMARY.

CULTIVATION EXPERIMENTS WITH VIRUS OF FOOT-AND-MOUTH DISEASE. PETER K. OLITSKY and LOUIS BOËZ, J. Exper. Med. **45**:833, 1927.

Multiplication of virus in vitro was not observed, but the optimum conditions for preserving the virus were determined.

STUDIES ON BACTERIOPHAGE OF D'HÉRELLE: ON THE PARTICULATE NATURE OF BACTERIOPHAGE. J. BRONFENBRENNER, J. Exper. Med. **45**:873, 1927.

When filtrates of lysed cultures (bacteriophage) are subjected to prolonged dialysis under osmotic pressure against water, the presence of the lytic agent can be detected outside the membrane only during the first few days. The residue remaining inside the membrane contains the bulk of the original lytic agent, and yet it is no longer capable of diffusing into the outer solution.

The interruption of diffusion is shown not to be due to any alteration in the permeability of the membrane. Moreover, the residue fails to diffuse through a fresh membrane of similar permeability, while the dialyzed portion of the phage passes quantitatively through a new membrane. When ultrafiltration under pressure was substituted for dialysis, the residue on the filter could be washed repeatedly with water without giving off into the filtrate any more active agent. However, if broth was substituted for water, a renewed diffusion of the active agent resulted.

These results are interpreted as indicating that the colloidal particles present in the lytic filtrates (and apparently endowed with properties of bacteriophage) do not represent autonomous units of the active agent, but merely serve as a vehicle on which the agent is adsorbed. They vary in size within limits wide enough to permit fractionation by means of ultrafiltration. When the coarser particles retained by the ultrafilter are washed with broth, some of the active agent is detached from its coarse vehicle particles. This agent, now more highly dispersed, is capable of passing the filter which held it back previously.

AUTHORS' SUMMARY.

THE MECHANISM OF LYSIS OF DEAD BACTERIA IN THE PRESENCE OF BACTERIOPHAGE. J. BRONFENBRENNER and R. MUCKENFUSS, J. Exper. Med. **45**:887, 1927.

We have been able to confirm the observations of Twort as well as of Gratia, that dead staphylococcus may undergo lysis if, in addition to a suitable bacteriophage, live staphylococcus is also present. Moreover, we have endeavored to ascertain the mechanism of this phenomenon and have found that, in order to elicit it, it is necessary to control the numbers of live and dead bacteria in the mixture. An excess of dead bacteria interferes with lysis by adsorbing the bacteriophage before it has the opportunity to initiate necessary changes in the live bacteria, so that all lysis is prevented. The phenomenon is specific, that is, the lysis of live bacteria is accompanied by lysis of dead bacteria of the same species only. Lysis of dead bacteria occurs best with staphylococcus, an organism which easily undergoes spontaneous autolysis under appropriate conditions. In the case of *B. coli* or *B. dysenteriae* the lysis of the dead bacteria is uncertain. Dead bacteria need not be present in the mixture at the beginning of the experiment; they will be dissolved if added any time before, during, or after the completion of lysis of live bacteria.

If the test is performed so that a suitable semipermeable membrane is interposed between the dead and the live bacteria, the dead bacteria are not dissolved, in spite of the lysis of live bacteria on the other side of the membrane. The agent determining the lysis of dead bacteria is not diffusible, while the principle initiating the lysis of live bacteria diffuses freely and is demonstrably present on both sides of the membrane. The complete independence of the agent causing dissolution of dead bacteria from bacteriophage can also be shown by separating the two agents by means of filtration, or by adsorption on bacteria.

The ferment-like substance responsible for the lysis of dead bacteria is different from the bacteriophage. It is not diffusible through collodion; it is easily adsorbed on clay filters; it is heat-labile, and is inactivated on standing.

An agent possessing identical properties was found in cultures of staphylococcus undergoing spontaneous autolysis in the absence of bacteriophage, but in this instance the agent appeared in the filtrates considerably later than it did when phage was present.

AUTHORS' SUMMARY.

INFECTION OF RATS BY GÄRTNER'S BACILLUS. C. RICE-JONES. J. Path. & Bact. **30**:45, 1927.

Rats can be infected readily with Gärtner's bacillus by feeding. The bacillus occurs in the spleen and liver of nearly all fed animals in about forty-eight hours, it begins to disappear after about ten days; after two months it can be recovered from only about 10 per cent. Specific agglutinins develop and may persist long after the bacilli have disappeared. Animals harboring bacilli can initiate an outbreak among fresh rats.

CHRONIC OR SUBACUTE HERPETIC MENINGO-ENCEPHALITIS IN THE RABBIT, WITH SOME OBSERVATIONS ON CALCIFICATION. C. DA FANO, J. Path. & Bact. **30**:67, 1927.

The authors claim to have produced a hitherto undescribed form of chronic or subacute herpetic meningo-encephalitis in rabbits by provoking in them a state of partial immunity to the virus of herpes or by attenuating the same virus in vitro prior to inoculation. All of the animals developed a typical herpetic syndrome, from which they recovered, to survive for varying periods of time. The state of improvement varied from almost complete recovery to conditions of semilethargy and apathy to mild acute manifestations.

Microscopically, the lesions show several forms: wide-spread meningeal, perivascular and parenchymatous infiltrations of a subacute or chronic type; severe changes in the different areas of the brain, including atrophy of nerve cells, disintegration of nerve tissue with accumulations of lipoid-laden phagocytes; true and pseudocalcification, and proliferative changes with tendency to heal.

Brains freshly removed from affected animals are noninfective, but when the brains are preserved in glycerol for certain periods, the virus of herpes can be recovered, and the disease can be transmitted to other rabbits. Little immunity is conferred on rabbits by this chronic form of encephalitis.

The authors believe that the chronic or subacute meningo-encephalitis of the rabbit resembles epidemic encephalitis in man, clinically, experimentally and histologically, more closely than does the acute experimental form of the disease.

E. M. HALL.

TRANSMISSION OF TRYPANOSOMIASIS IN RABBITS. HILDA A. CHANNON and HEDLEY D. WRIGHT, J. Path. & Bact. **30**:253, 1927.

Trypanosomiasis of wild and tame rabbits occurs spontaneously, and the infection *(T. nabiasi)* appears to be transmitted by the rabbit flea.

VARIANT COLONIES OF STAPHYLOCOCCUS AUREUS. JOSEPH W. BIGGER, C. R. BOLAND and R. A. O'MEARA, J. Path. & Bact. **30**:261, 1927.

By growing *Staphylococcus aureus* in broth, variants can be secured on agar plates showing alteration in color, texture and cohesion.

PSEUDOHEMOLYTIC STREPTOCOCCI IN THE SPUTUM OF PULMONARY TUBERCULOSIS. W. M. CUMMING, J. Path. & Bact. **30**:279, 1927.

The main point of distinction between hemolytic and pseudohemolytic streptococci appears to be the failure of the pseudohemolytic to produce hemolysin in serum broth. Of 119 patients with pulmonary tuberculosis, 89 had the pseudohemolytic kind in the sputum and 22 the ordinary hemolytic streptococci.

SPIROCHETAL JAUNDICE. G. BUCHANAN, Special Report Series, No. 113, Medical Research Council, London, 1927, p. 64.

Twenty-two cases of spirochetal jaundice in Scotland have been studied in detail. Most of the cases occurred in coal-miners, and in this group the death rate was 29 per cent. The main changes at autopsy were a general, intensely yellow color of the integuments, cutaneous petechiae, and hemorrhages more or less widely distributed but particularly noticeable in the stomach. There was degeneration in the kidney and liver with necrosis. In the spleen and lymph nodes, phagocytosis of the red cells was noted. Spirochetes were difficult to find in the tissues. In seventeen cases, spirochetes were found in the urine. Infected guinea-pigs succumbed early, and a relative small lymptocytosis developed within a few days after infection—a new observation. In guinea-pigs, spirochetes were found easily after death and the lungs presented a characteristic "spotted" or "butterfly-wing" appearance. Of 166 wild rats examined, 36.7 per cent proved to be infected. The facts point to human infection by way of skin abrasions, the eye and the nose rather than by ingestion. Spirochetal organisms were found in the fungal slime hanging from the roof as well as in surface and pit waters of coal mines. Such organisms caused typical disease in two guinea-pigs. Extermination of rats is the main preventive measure.

THE ORIGIN OF ACETALDEHYDE IN BACTERIAL AND ANIMAL METABOLISM. M. D. WHETHAM, Australian J. Exper. Biol. & M. Sc. **4**:35, 1927.

Whetham presents a wide and critical survey of the subject to date, including hitherto unpublished observations on work from the Cambridge School on the metabolism of "resting" bacteria.

The two theories of carbohydrate metabolism (Neuberg's pyruvic acid-acetalderyde theory and Lusk's methylglyoxal-lactic acid or methylglyocal-acetaldehyde and formic acid theory) are thoroughly examined on the basis of evidence taken from bacterial and animal metabolism and from perfusion and tissue-oxidation experiments. Many new facts are adduced in favor of Lusk's theory of aerobic oxidation, notably the widespread formation of formic acid in carbohydrate oxidations. The origin of the acetaldehyde is discussed and the synthesis of higher fatty acids from the acetic acid resulting from oxidation of the acetaldehyde is shown from numerous examples to be of great importance, the need for investigation of the fate of acetic acid being stressed. The fate of the pyruvic acid in the Neuberg type of metabolism and the relation of pyruvic acid and acetaldehyde in bacterial and animal metabolism is critically considered. There is a complete bibliography of ninety-seven references.

C. S. HICKS.

DIPHTHERIA TOXINS PRODUCING A DIPHTHEROID BACILLUS. P. HAUDUROY, Compt. rend. Acad. d. sc. **184**:409, 1927.

There is a filtrable form of the diphtheria bacillus which may be identical with the toxic principle found in the sterile filtrates of broth cultures of this organism. The filtrable form may be isolated and grown by inoculation of the toxic filtrate into an especial medium found successful for the cultivation of other filtrable forms. It reverts by fusion into a nontoxicogenic diphtheroid modification.

ARTHUR LOCKE.

PROBLEMS IN DIPHTHERIA. I. THE BIOLOGY OF THE CORYNEBACTERIA AND THE QUESTION OF VARIABILITY. M. GUNDEL, Centralbl. f. Bakteriol. **101**:337, 1927.

Gundel claims that in the animal body diphtheria bacteria may become transformed into pseudodiphtheria bacilli and that in vitro these may be changed back into true diphtheria bacilli. In vitro, a pathogenic diphtheritic strain may be trans-

formed to a nonpathogenic strain and vice versa, and a pseudodiphtheritic strain into a nonpathogenic diphtheritic strain. He feels that the virulence test of diphtheritic strains in guinea-pigs is no criterion as to their virulence for human.

PAUL R. CANNON.

BACTERIOLOGIC STUDIES OF STRAINS OF STREPTOTHRIX MENINGEA. MICHELE GERBASI, Centralbl. f. Bakteriol. **101**:369, 1927.

Gerbasi reports a study of six strains of a streptothrix isolated from the spinal fluid of patients with meningitis. The morphologic and biologic characteristics are described.

PAUL R. CANNON.

A FAULTY DIAGNOSIS OF RABIES? WALDEMAR LOEWENTHAL, Centralbl. f. Bakteriol. **101**:393, 1927.

Loewenthal reports a case of a cat with symptoms of rabies and in which definite Negri bodies were present, yet a heavy emulsion of the brain injected intracerebrally into two rabbits had no effect.

PAUL R. CANNON.

THE ETIOLOGY OF HERPES. WALDEMAR LOEWENTHAL, Centralbl. f. Bakteriol. **101**:396, 1927.

Loewenthal presents an illustrated cytologic study dealing with the so-called herpes bodies in the cornea of rabbits and in the vesicles of patients.

PAUL R. CANNON.

THE PARASITE OF RABIES. F. PAUL and F. SCHWEINBURG, Virchows Arch. f. path. Anat. **262**:164, 1926.

The Negri body is generally accepted as specific for rabies, although the exact nature of the body is still a matter of controversy. According to some, it is a degeneration product, composed in part of material derived from the nucleolar substance of the degenerating ganglion cell. Prowachek believed that the minute blue-staining bodies within the Negri body are the actual parasites and that the eosin-staining ground substance in which the granules lie is derived from the infected cell — hence the name chlamydozoa or mantle animalcules. In 1924, Manouélian and Viala described as *Encephalitozoon rabiei* what they considered the protozoan parasite of the disease and held it to be distinct from the Negri body. Paul and Schweinburg examined 117 negri-positive brains by the method of Manouélian and Viala, as well as by a number of other methods. They were unable to confirm the work of the latter observers, and held that the supposed parasites of a distinct species are various stages in the cycle of development of the Negri body; the latter beings as a minute, just barely visible granule, which increases in size and may then break up again into minute granules. Ultimately, the large, typical, rather complex Negri body is formed. Division of this or any process corresponding to sporulation was not seen. The authors conclude that the Negri body is not a degeneration product but is the parasite of rabies, and that the entire body, and not merely the contained granules, is the parasite. That the parasite is a protozoon has not been proved.

O. T. SCHULTZ.

A COMPARATIVE STUDY OF CHICKEN AND PIGEON POX. T. SAITO, Ztschr. f. Immunitätsforsch. u. exper. Therap. **48**:451, 1926.

Saito describes a comparative study of two strains of virus of chickenpox and two of pigeonpox. Chickenpox virus, when it "takes" in the pigeon, causes a reddening and swelling of the skin with small nodules. The virus, however, can

be transmitted to other pigeons and causes a spreading eruption. This passage attenuates it for the chicken. When pigeonpox virus is applied to the skin of a chicken, the reaction is slight. Further passage makes the reaction even weaker, but the virulence for the pigeon remains unchanged. There is a clear-cut reciprocal immunity, however, each of the species being made immune to both viruses by immunization with one.

PAUL R. CANNON.

THE PROBLEMS OF THE ROADS OF INFECTION. H. BEITZKE, Ztschr. f. Tuberk. **47**:18, 1927.

In a controversy with Huebschmann, the author reiterates previous statements to the effect that aërogenous exogenous reinfection plays the all important rôle in the development of pulmonary tuberculosis. One of Huebschmann's statements that the primary focus hardly ever is found in the apex is refuted by the detailed report of three such cases. The frequency of the exogenous reinfection is revealed by the fact that in tuberculosis in childhood about 10 per cent of the cases are due to the bovine type of bacillus; that, however, in pulmonary tuberculosis of adults only three cases due to the bovine type are known in the literature. The predilection of the apexes for the localization of reinfecting bacilli is explained by a local disposition due to lack of aeration and the slow flow of lymph.

MAX PINNER.

REMARKS TO THE PRECEDING ARTICLE BY H. BEITZKE. P. HUEBSCHMANN, Ztschr. f. Tuberk. **47**:23, 1927.

The occurrence of a few primary foci in the apexes is only the exception to the rule. Similarly, reinfections by aspiration may at times occur in the apex, but the frequency of these occurrences is not more than 1 in 100. The author promises to publish in the near future observations on the distribution of coal dust in different parts of the lung in incipient stages of anthracosis, which will support his view that aspiration of foreign particles into the lung results in a deposition which leaves the apexes practically free.

MAX PINNER.

A CASE OF PRIMARY EXTRAPULMONARY TUBERCULOUS INFECTION WITH NONSPECIFIC GIANT CELL PNEUMONIA. E. NOWOTNY, Ztschr. f. Tuberk. **47**:25, 1927.

In a boy, aged 1½, a tuberculous primary complex in the region of the head or neck was observed, whose lymphogenous component was well developed, whereas the primary focus could not be determined with certainty. This case proves again previous statements from Ghon's school that the primary focus may heal while the lymphogenous component caseates. The lungs in this case showed diffuse catarrhal bronchitis and bronchiolitis, extensive atelectasis and lobular pneumonia in the posterior and basal parts of the left lower lobe, and to a lesser extent in the right lower lobe; scattered atelectatic and lobular pneumonic foci were found in both upper lobes and in the right middle lobe; there was a fibrinous pleuritis in the right lower region. Microscopically, the bronchi showed the picture of a purulent bronchitis and bronchiolitis, with extensive desquamation of the epithelium. The alveoler sacs were filled with cellular exudate containing polymorphonuclear leukocytes, swollen epithelial cells, a few round cells and isolated round multinucleated giant cells. The number of nuclei in these cells varied between 6 and more than 100. No tuberculous alterations were found in the lung. The author is inclined to believe that these giant cells were derived from alveolar epithelial cells. Etiologically, a whooping cough, which still persisted at the time of death, may have been of importance.

MAX PINNER.

Immunology

COMPLEMENT FIXATION IN TUBERCULOSIS. PAUL A. LEWIS, J. Exper. Med. **45**:701, 1927.

Prolonged extraction of tubercle bacillus with boiling ethyl alcohol, followed by reprecipitation by chilling the hot solution yields an active complement fixing substance, which gives precipitate with high dilutions of heated normal blood serum of a number of species. The reaction is apparently not influenced by immunization and is marked by a long prozone.

IMMUNITY TO PNEUMOCOCCUS MUCOSUS (Type III). WILLIAM S. TILLET, J. Exper. Med. **45**:713, 1927.

Type III pneumoccoci failed in most cases to stimulate the formation type specific antibodies (anti-S antibodies), but were effective in stimulating the production of non-type specific antibodies (anti-P antibodies). These antibodies were unable to protect mice.

THE IMMUNOLOGIC BEHAVIOR OF MUCOIDS. JULIAN H. LEWIS and H. GIDEON WELLS, J. Infect. Dis. **40**:316, 1927.

Mucoids from eggs and from blood are antigenic, but less so than most other proteins of equal solubility. This may depend on the vigorous treatment required for their isolation. Mucoids from the eggs of several species of birds show some immunologic relationship, but can generally be distinguished from each other by quantitative results or saturation experiments, especially by the uterine strip method of Schultz and Dale. Most closely related to each other are the ovomucoids from goose and duck eggs, which are perhaps identical. Hen and guinea-fowl ovomucoids are also closely related. Ovomucoid from turtle eggs is less closely related to the avian ovomucoids than these are to each other. Seromucoids from sheep, beef and dog blood seem to be easily distinguishable from one another, and they show but little relationship to the ovomucoids.

AUTHORS' SUMMARY.

IMMUNOLOGIC REACTIONS OF THE GLOBULINS FROM THE SEEDS OF LEGUMINOUS PLANTS. THE BIOLOGIC REACTIONS OF THE VEGETABLE PROTEINS. IX. H. GIDEON WELLS, JULIAN H. LEWIS and D. BREESE JONES, J. Infect. Dis. **40**:326, 1927.

Immunologic studies have been made of the alpha and beta globulin fractions of several leguminous seeds, namely, navy, mung, adzuki, lima and Georgia velvet beans. These two protein fractions are chemically distinct from each other as obtained from each of the five species of beans, the most marked difference being that the alpha globulins have a higher sulphur and usually a lower nitrogen content. The alpha and beta fraction of the five different beans when compared with one another show some chemical similarities and some differences.

Immunologic tests brought out more clearly these relationships and differences. Anaphylaxis shock reactions, uterine strip anaphylaxis reactions and complement fixation reactions were used with all these proteins, and in general confirmed each other, but the uterine strip reaction was found to give the most accurate differentiation of the proteins, especially when these were admixed with one another. Only by this method was it possible to show conclusively that our several preparations of alpha and beta globulins contain

admixtures of two distinct antigens, confirming the chemical evidence that there are two distinct globulins in each species of bean.

The globulins from adzuki and mung beans were found to be distinct from the globulins of navy, lima and Georgia velvet beans, but the alpha and beta globulins of adzuki and mung beans seem to be either identical with or similar to each other. This immunologic similarity is found to correspond to a close chemical similarity according to such methods as are available for the study of protein chemistry.

Georgia velvet bean globulins were found to be distinct immunologically from the globulins of the four other species of beans tested. This may be related to the fact that chemically these globulins have a higher nitrogen content than the others, and a larger proportion of alpha globulin. Botanically the Georgia velvet bean is one of the Stizolobia, and the other four beans belong to the Phaseolus group.

The globulins of the lima and navy beans, although closely related to each other, were found to be distinct from the globulins of mung, adzuki and Georgia velvet beans. Nevertheless the lima and navy bean globulins are distinguishable from each other by the delicate uterine strip method.

AUTHORS' SUMMARY.

EFFECT OF TYPE 1 PNEUMOCOCCUS BROTH CULTURE ON THE PROTECTIVE ACTION OF TYPE 1 ANTISERUM. G. M. SICKLES, J. Infect. Dis. **40**:369, 1927.

There is present in type 1 pneumococcus culture broth a substance in the presence of which the protective action of type 1 pneumococcus serum is diminished. The substance serum, relatively thermostable, deteriorates with age, and is not absolutely type specific. It is not present in very young cultures in a sufficient amount to be detected by the method used, but it begins to appear about the eighth hour of incubation. When the pneumococcus culture broth and antiserum are exposed together to a temperature between 40.5 and 41 C. the inhibiting effect of the broth on the protective action of the serum is considerably diminished. When type 1 serum is diluted with broth and used as a culture medium for type 1 pneumococcus, the protective action of the serum is neutralized or destroyed.

AUTHOR'S SUMMARY.

THE INTRACELLULAR PROTEINS OF BACTERIA. 2. THE GLOBULINS AS INDICATORS OF INTERSPECIES RELATIONSHIPS. CASPER I. NELSON, J. Infect. Dis. **40**:412, 1927.

Globulins obtained from seven species of the colon-typhoid group of bacteria were effective antigens for the production of precipitins in rabbits. These globulins are highly specific for their homologous antiserums. They also possess a specificity for heterologous serums which is quantitatively proportional to the genetic relationship which the heterologous derivative bears to the homologous one. The data of complete direct and cross precipitin titrations of the bacterial globulins and their antiserums, when analyzed objectively and statistically, yield a sequence of interspecies relationship about as follows:

Group A	1. *B. typhosus*
	2. *B. paratyphosus* A
Group B	3. *B. paratyphosus* B (Aertrycke type)
	4. *B. enteritidis*
Group C	5. *B. coli*
Group D	6. *B. dysenteriae* Flexner
	7. *B. dysenteriae* Shiga

This is quite in agreement with the latest opinions concerning the host distribution of this group. Two distinct groups of organisms are recognized, the dysentery group and the typhoid-paratyphoid A group. There is a third less well defined group, the enteritidis-paratyphoid B group. A fourth group is represented by *B. coli* which is linked in a fundamental way with all the other organisms and particularly with the dysentery group. *B. coli* genetically speaking, is a stem organism.

AUTHOR'S SUMMARY.

PURIFICATION OF ABORTIN. P. SCHOENHOLZ and K. F. MEYER, J. Infect. Dis. **40**:453, 1927.

Cutaneous hypersensitiveness in abortus-infected guinea-pigs may be demonstrated by testing the infected animal intracutaneously with filtered cell solutions of *Br. abortus*. The substance precipitated by acetic acid in the cold at p_H 3.5 to 4 elicits allergic reactions as effectively as the original solution. The neutralized supernatant, both unheated and heated, devoid of this acid-precipitable substance, is ineffective. Digestion with trypsin destroys the activity of the acid-precipitable protein.

AUTHORS' SUMMARY.

THE SPECIFICITY OF THE WEIL-FELIX REACTION IN BRILL'S DISEASE. LEON C. HAVENS, J. Infect. Dis. **40**:479, 1927.

Results obtained with the macroscopic Weil-Felix test in more than 100 cases of Brill's disease indicate that the reaction is elicited in about 95 per cent of cases during the second week or later. It is usually negative during the first week, becoming increasingly stronger until convalescence. Tests including more than 1,000 negative results demonstrate its specificity. Agglutination of *B. proteus* X19 in dilutions higher than 1:80 has not been obtained in other disease conditions. The microscopic Weil-Felix test with dried blood has yielded false positive results, and, for this reason, is of doubtful value. The agglutinins for *B. proteus* X in serums from patients with Brill's disease and also in serums from rabbits after injection of guinea-pig brain virus are relatively thermolabile: they are destroyed by heating the serum at 62 C. for 1 hour.

AUTHOR'S SUMMARY.

STANDARDIZATION OF BACTERIAL VACCINES BY PHOTOMETRIC METHODS. ADELAIDE B. BAYLIS, J. Infect. Dis. **40**:497, 1927.

Further experience with the photometric estimation of bacterial vaccines confirms the previous statement that this method offers precise accuracy combined with economy. Observations on the absorption and diffuse produced by standardized suspensions of the paratyphoid bacilli are here recorded. This data together with the similar data concerning the typhoid bacillus presented in the previous communication afford criteria for the photometric standardization of the components of the typhoid-paratyphoid vaccine. Photometric standardization of bacterial vaccines also offers a check on variation in the average size of organisms in different cultures.

AUTHOR'S SUMMARY.

SOLUBLE ANTIGENS OF BACTERIUM ENTERITIDIS. SARA E. BRANHAM AND ELEANOR M. HUMPHREYS, J. Infect. Dis. **40**:516, 1927.

Bacterium enteritidis can be cultivated in a synthetic medium free from protein. Berkefeld filtrates, free from bacteria, obtained after from eight to fourteen days' incubation, are extremely toxic for rabbits when given intravenously.

These filtrates, when injected into rabbits, stimulate the production of agglutinins, precipitins, complement-fixing antibodies, and possibly antitoxins.

The antigenic properties of these filtrates are increased when the liquids are concentrated by evaporation in vacuo. The products so obtained are better antigens than suspensions of *Bacterium enteritidis*. Protein cannot be demonstrated even in the dry residue obtained by the evaporation of such a filtrate. An opalescent fluid and a gray precipitate are obtained when this dry residue is dialyzed. Protein cannot be demonstrated in either of these fractions. The precipitate contains carbohydrate. Further concentration of the opalescent fluid gives a liquid that gives faintly positive reactions for tryptophane and histidine, and a faintly positive ninhydrin reaction. Protein was therefore possibly present. An amount of filtrate that could, at most, have contained 0.000,003 to 0.000,004 Gm. of protein led to definite antibody formation. Whether or not so small an amount of protein can, in fact, be held exclusively responsible for this antibody production may be questioned. Such a possibility should, however, be borne in mind in interpreting results obtained with apparently protein-free materials.

AUTHORS' SUMMARY.

URTICARIA AND AUTOINFECTION IN STRONGYLOIDOSIS. F. FÜLLEBORN, Arch. f. Schiffs- und Tropen- Hyg. **30**:732, 1926.

A great majority of the strongyloides carriers observed by Fülleborn presented large itching urticarial wheals in the anal region. Strongyloides larvae, that have developed from remnants of feces, penetrate the skin in the anal region, which seems to possess a marked hypersensitiveness. This penetration by larvae produces a new permanent focus of infection and contributes to the long duration of human intestinal strongyloidosis; in one case twenty-four years. Except for itching, the skin lesions caused by the larvae are of little importance and disappear rapidly. The larvae penetrate a young and delicate skin more easily than a skin that is rough and old. In these patients urticarial wheals could be provoked by scratching the skin, although they may have been absent for weeks.

IMMUNIZATION AGAINST RABIES OF THE DOG WITH LYSSIN. H. MIESSNER and G. BAARS, Centralbl. f. Bakteriol. **101**:79, 1927.

The authors describe experiments aiming at the immunization of dogs against rabies and have succeeded by the subcutaneous injection with lyssin, which is a dried rabies virus, prepared according to the method devised by Miessner in 1912. This lyssin retains its immunizing properties for at least sixty days, and the injection protects again an intramuscular injection of street virus. The immunity lasts at least for one year.

PAUL R. CANNON.

THE PASSIVE TRANSFERENCE OF HYPERSENSITIVENESS TO CHEMICALLY KNOWN SUBSTANCES. HANS BIBERSTEIN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **48**:297, 1926.

Biberstein has succeeded by means of the Prausnitz-Küstner method in transfering hypersensitiveness to mercury, arsphenamine bismuth, and a brand of amidopyrene U. S. P. The results were negative with arsenic, formol, iodine, potassium iodide, acetylsalicylic acid and phenacetin.

In three cases of dermatitis caused by arsphenamine another person was sensitized to arsenic. In one case, it was possible to obtain a local hypersensitivity to a mercuric chloride-serum solution, which was manifested both against the solution and against mercury.

PAUL R. CANNON.

THE EFFECT OF IMPURITIES IN SODIUM CHLORIDE ON HEMOLYSIS. S. J. GINSBURG and W. S. KALININ, Ztschr. f. Immunitätsforsch. u. exper. Therap. **49**:62, 1926.

The presence of sulphates or chlorides of calcium or potassium greatly hinders hemolysis. The authors think that the variability in results in Wassermann tests many times is due to the use of an impure sodium chloride.

PAUL R. CANNON.

THE BIOLOGIC PROPERTIES OF FIXED VIRUS. M. ISABOLINSKY and A. ZEITLINA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **49**:67, 1926.

According to the authors, glycerol is the best preservative for the fixed virus, the latter retaining its activity in 80 per cent glycerol for fifteen days. The subcutaneous injection in rabbits of this virus in the manner used for immunization in man leads to a marked insusceptibility to the subsequent subdural injection of brain emulsion from a rabbit infected with rabies. The authors conclude that the injection of the fixed virus leads to its accumulation in the central nervous system, where it leads to the formation of specific antibodies.

The blood of rabbits immunized with fixed virus contained no protective bodies against active rabies virus, showing that the immunity to rabies is a local type, appearing in the nervous system.

PAUL R. CANNON.

EXPERIMENTAL STUDIES OF PRECIPITIN AND SPECIFIC CUTIREACTION. VI. THE PRECIPITIN IN THE TISSUE PRESENTING CUTIREACTION (ARTHUS PHENOMENON). G. SHOGI, Acta Dermatol. **8**:483, 1926.

The extracts of tissue excised from twenty-four to forty-eight hours after a reinjection of the specific antigen into the skin of an immune rabbit, the tissue presenting specific cutireaction, contained little or no precipitin. In the tissues excised three or four days after the reinjection, the precipitin had increased and the antigen had disappeared. In rabbits immunized with two antigens, egg white and serum (human, horse or sheep) and given separate reinjections of each antigen on opposite sides, the reacting tissues in each instance yielded extracts with little or no precipitin for the protein used at that site but with precipitin for the other protein of nearly the same titer as that of the blood serum.

EXPERIMENTAL STUDIES OF PRECIPITIN AND SPECIFIC CUTIREACTION. VII. HISTOLOGICAL FEATURES OF THE SPECIFIC CUTIREACTION IN IMMUNIZED RABBITS. G. SHOGI, Acta Dermatol. **9**:77, 1927.

The specific cutireaction following the reinjection of antigen in immune rabbits is an acute inflammatory process localized at the site of reinjection with marked infiltration of polymorphonuclear leukocytes and sometimes hemorrhage, which often terminates in partial necrosis of the tissue. The climax of the cutireaction is reached about twenty-four or forty-eight hours after the injection and with certain individual variations the intensity parallels the height of the immunity.

THE RESORPTION OF HETEROGENOUS PROTEINS FROM THE MUCOUS MEMBRANE OF THE URINARY BLADDER. G. SHOGI, Acta Dermatol. **9**:100, 1927.

From precipitin tests of blood serum for antigen (human, horse or sheep serum) injected into the bladder (carefully after catheterization) and left for

six hours, it appeared that human serum more than the others was absorbed in normal rabbits which after repeated treatments produced precipitin. Immune rabbits from whose blood precipitin had disappeared responded by rise in titer after bladder injections of the specific antigen (egg white, or serum), so it was concluded that small amounts were resorbed.

Tumors

CARCINOMA FROM THE PAROTID DUCT. J. L. GOFORTH, Am. J. M. Sc. **173**:624, 1927.

The unusual occurrence of a carcinoma in the parotid duct is recorded. The tumor was associated with a peculiar, calculus-like structure. In the salivary system the association of calculus and carcinoma is extremely rare.

CARCINOMA OF BOTH BREASTS IN A WOMAN UNDER TWENTY YEARS OF AGE. L. W. KRAUSS and B. S. KLINE, Am. J. Surg. **1**:277, 1926.

A girl, aged 16 years, entering Mt. Sinai Hospital, Cleveland, on Jan. 4, 1922, for the correction of deformities of the leg also had pain and swelling of the left breast and a bloody discharge from the nipple. The tumor, 7 cm. in diameter, well encapsulated and directly under the nipple, was removed and microscopically proved to be a cystadenoma with epithelial extensions into the regional stroma and breast. On June 24, 1923, cystlike masses were removed from the right breast, and in sections of these were changes characteristic of chronic mastitis, papillomatous cysts and early systadenoma. On April 17, 1925, a radical amputation of the left breast was performed for papillary cystadenocarcinoma with metastases to the axillary lymph glands. The view advanced is that of a primary origin of carcinoma on each side within papillomatous cysts following chronic mastitis.

GEORGE RUKSTINAT.

RHABDO-MYOSARCOMA OF THE VULVA IN CHILDREN. C. D. LOCKWOOD, Arch. Surg. **14**:860, 1927.

There are forty-one cases of this tumor on record. The case described was in a child, aged 16 months. The tumor was first diagnosed endothelioma or spindle cell sarcoma, and treated with radium. In nine months abdominal metastases occurred. Post mortem, tumors were found in the abdomen, pericardium and left lung. The structure was rather myxomatous with large spindle cells containing cross and longitudinal striations.

N. ENZER.

INACTIVATION OF CHICKEN TUMOR VIRUS BY CARMINE. MARGATET R. LEWIS and HOWARD B. ANDERVONT, Bull. Johns Hopkins Hosp. **40**:265, 1927.

It is concluded that the active agent in extracts of tumors of chickens in inactivated by carmine through adsorption of the virus by carmine particles.

INCIDENCE OF CARCINOMA OF THE UTERUS AMONG JEWISH WOMEN. A. HORWITZ, Surg. Gynec. Obst. **44**:355, 1927.

Although most authorities agree that cancer of the uterus is comparatively less common among Jewish women than among Gentile women, there are a few who question such a conclusion. Horwitz, analyzing the admissions at the Mayo Clinic from 1920 to 1925, finds only ten cases of carcinoma of the uterus in Jewish women, and 1,227 cases in Gentile women. Ninety-seven per cent of the patients

were married. From data obtained at the Curie Hospital, where two thirds of the patients were treated for carcinoma by roentgen rays or radium, the incidence of carcinoma was slightly less for the Jewish patients. He concludes that carcinoma of the uterus is comparatively infrequent among Jewesses, being about one fourth as frequent as in Gentile women. Carcinoma of the breast in the female is common among Jewesses and almost equals the percentage in Gentile women, the incidence being 26.4 and 28.3 per cent, respectively. Carcinoma of the digestive tract, including the liver and pancreas, was almost twice as frequent in the Jew as in the Gentile, being 30.2 and 17.1 per cent, respectively.

M. L. PARKER.

THE EFFECT OF ULTRA-VIOLET RAYS ON THE ROUS CHICKEN SARCOMA. F. W. ILLINGWORTH and G. L. ALEXANDER, J. Path. & Bact. **30**:365, 1927.

The "agent" of the Rous chicken sarcoma, present in cell-free filtrates of the tumor, is susceptible to irradiation from a tungsten arc, the invisible ultraviolet rays being chiefly or entirely responsible for this action. The Rous "agent" survives a longer exposure to the rays than do common bacteria in dilute suspension. Inactivation of the Rous "agent" by ultraviolet rays is not associated with change of hydrogen ion concentration, and there is no evidence to suggest that it is due to the formation of formaldehyde, or any other product of decomposition. We have been unable to detect the presence of either of the factors described by Gye in filtrates after irradiation.

AUTHORS' SUMMARY.

PAGET'S DISEASE OF THE NIPPLE AND ITS RELATIONSHIPS. ROBERT MUIR, J. Path. & Bact. **30**:451, 1927.

Paget's disease, as usually met with, is the result of the invasion of the epidermis of the nipple by tumor cells of glandular type which reach it from the upper extremities of the lactiferous ducts affected by neoplastic disease. These tumor cells constitute the "Paget cells"; their growth is intra-epidermal. The invasion of the epidermis leads to reactive changes in the underlying connective tissue—infiltration of plasma cells, etc., new formation of capillaries, congestion with serous exudate. In this way the characteristic appearance of the nipple results; later, the superficial layers of epithelium may become destroyed and this process may spread. The disease of the ducts which may be spoken of as "intraduct carcinoma" may be said to have a low degree of malignancy, since it may affect systems of ducts and even spread to the acini without breaking through the normal confines. The growth of the tumor cells is in the first instance intra-epithelial, and in the larger ducts and sinuses much proliferation may occur before the internal lining is actually broken. This mode of growth is comparable with that seen when the cells reach and infiltrate the epidermis. The growth within the ducts or acini may ultimately break through and then an ordinary infiltrating cancer results. Both Paget's disease and ordinary carcinoma are thus possible sequels of the same disease—intraduct carcinoma.

AUTHOR'S SUMMARY.

A FILTRABLE ENDETHELIOMA OF THE FOWL. A. M. BEGG, Lancet **1**:912, 1927.

The tumor can be propagated by cellular grafts, by dried material, and by filtrates in broth of suspensions of tumor tissue. Gye's conception of the dual nature of noncellular transmission is supported by the results of experiments with this tumor.

BILATERAL TUMORS IN A PIGEON HAVING THE STRUCTURE OF THE SUPRARENAL CORTEX. ROSARIO MARZIANI, Tumori. **12**:379, 1926.

The author accidentally found in a pigeon bilateral tumors in the region of the suprarenals which weighed 1.5 and 1 gr., respectively, and which had the structure of the suprarenal cortex. The right tumor was firmly attached by a prolongation to the vena cava inferior. The suprarenals were not found. No metastases were discovered.

W. OPHÜLS.

ACTION OF INSULIN ON TRANSPLANTED TUMORS. S. CIOFFARI and N. PICCALUGA, Tumori **12**:387, 1926.

Mice inoculated with tumors and treated with insulin are more resistant to the development of the tumors than animals that were not treated. This resistance is particularly noticeable during the first period of growth of the implanted tumors. It may be increased by preliminary treatment of the animals with insulin. The growth of the implanted tumors is never completely inhibited. Inactivation of the insulin by boiling destroys its effect on the growth of the tumors.

W. OPHÜLS.

MICROSCOPIC OBSERVATIONS ON AN ADENOCARCINOMA OF THE BREAST. GIOVANNI GIULIANI, Tumori **12**:420, 1926.

Roentgen rays act not only on the tumor, but also on the normal tissues. The operative wound produced by the removal of a tumor which had recurred, healed slowly, indicating trophic disturbances due to the irradiation. At the present time an elective complete destruction of malignant tumor is impossible. In spite of this, all possible efforts should be made by physicists, constructors and physicians to improve roentgen-ray treatment.

W. OPHÜLS.

TWO RARE TUMORS OF THE BREAST (PAGET'S DISEASE AND PERITHELIOMA). V. GHIRON, Tumori **12**:452, 1926.

A case of Paget's disease is described and also a rare tumor of the mamilla which is interpreted as a perithelioma.

W. OPHÜLS.

CLINICAL AND HISTOLOGIC STUDY OF SO-CALLED SEBACEOUS ADENOMA (PRINGLE-BALZER'S TUMOR). F. FLARER, Tumori **12**:468, 1926.

Flarer reports two cases of multiple small tumors of the skin of the face which exhibit the usual gross and microscopic characteristics of the so-called adenoma of the sebaceous glands. He does not believe that this designation of the growths is a proper one and thinks that the noncommittal term "multiple symmetrical nevi" is preferable.

W. OPHÜLS.

ORIGIN OF CHORIO-EPITHELIOMA. E. BOSTROEM, Beitr. z. path. Anat. u. a. allg. Pathol. **76**:293, 1927.

Boestroem, of Giessen, devotes ninety pages to a cytomorphologic study of chorio-epithelioma, for which he deduces an origin different from that usually held. He passes the successive stages in the development of our knowledge of this neoplasm in rapid review, beginning with Marchand's view, now generally accepted, that chorio-epithelioma of the uterus is derived from the fetal ectodermic epithelium of the chorionic villi. He traces the belief that tumors developing in the

female elsewhere than in the uterus, and often long after pregnancy, are derived from transplanted chorionic epithelium which has lain dormant but viable; the origin of testicular chorio-epitheliomas from trophoblastic epithelium of dermoids, and lastly the extragenital tumors of males from dermoids situated elsewhere. He concludes that hypotheses have been pyramided on each other until physicians have come to accept as facts, statements for which there is no warrant. He enunciates as a fundamental doctrine the statement that differentiated cells are incapable of division; that new cells, normal as well as abnormal, must therefore arise from indifferent mother cells, and that for the nonepithelial tissues the mother cells constitute a mesenchymal germinal tissue which is widely distributed throughout the body. Bostroem accepts as useful Marchand's employment of the term "typical" for those chorio-epitheliomas composed chiefly of syncytium like that of the trophoblast, and "atypical" for those composed of individual cells which have been likened to the chorionic wandering cells of the decidua basalis.

But while accepting these terms as expressive of morphologic differences, Bostroem derives none of the chorio-epitheliomas from chorionic or trophoblastic epithelium, but from subendothelial mesenchymal germinal tissue, especially such as is situated about the capillaries. In the "typical" form of tumor the perivascular mesenchyme of the larger capillaries gives rise to the "primary" tumor cells, which are united with each other to form a multinucleated syncytium. Within the latter occurs the endogenous formation of differentiated cells, which are round or polyhedral, sharply defined, have a finely vacuolated cytoplasm and a relatively large vesicular nucleus, and bear a resemblance to Langhans cells. In the "atypical" form of tumor, the mesenchymal germinal tissue about the smaller capillaries gives rise to "primary" tumor cells, which are sharply defined, have a deeply staining cytoplasm and a polymorphic, deeply staining nucleus and look like chorionic wandering cells. Within such cells occurs the endogenous formation of more faintly staining cells with vesicular nuclei. In both types of tumor the endogenous formation of the individual, so-called typical tumor cells from the "primary" ones continues by amitosis until the chromatin of the deeply stained nuclei has been used up. The finished cells then undergo a single mitosis and die. The stages in the life cycle of the tumor cell are the formation of the "primary" tumor cell from indifferent mesenchyme, the endogenous formation of cells which become differentiated, a single mitosis and death. The growth of the neoplasm cannot therefore be due to the unlimited multiplication of the original "primary" tumor cells first formed from the mesenchyme, but must be due to the progressive and continuous new formation of "primary" tumor cells from the indifferent mesenchyme. The so-called metastases of chorio-epithelioma are not formed from embolic derivatives of the primary tumor, but arise in situ from the pericapillary mesenchymal tissue of the involved organ. Since indifferent mesenchyme is widely distributed throughout the body, the genesis of chorio-epithelioma proposed by Bostroem explains, according to him, the occurrence of this form of tumor not associated with pregnancy, or in organs other than the uterus, or in the male, and its multiple occurrence. What is not explained is the reason for the greater frequency of the peculiar blastomatous proliferation of the mesenchyme in relation to pregnancy and its greater frequency in the female, although hints are given of an endocrine factor. The author promises in a future communication to attempt to show that the so-called epithelium of the chorionic villi is not derived from fetal ectoderm but from maternal mesenchyme, and to discuss the relation of lutein tissue to chorio-epithelioma and to the chorio-epithelial transformation of mesenchyme.

O. T. Schultz.

TREATMENT OF TUMORS WITH YEAST. G. H. JACUBSON, Ztschr. f. Krebsforsch. **24**:364, 1927.

Starting with the assumption that the disappearance of malignant tumors which occasionally follows erysipelas is due to the local asphyxia of the tumor cells, caused by the formation of carbon dioxide from glycogen by the streptococcus, the author used a variety of species of yeasts in the treatment of rats with transplantable Flexner-Jobling tumors. Intravenous injection of the yeasts caused rapid necrosis of the tumors, which was followed by inspissation of the necrotic material and final disappearance of the tumor. Metastases were similarly affected. Recurrence was rare, and some of the rats had lived nine months apparently cured.

O. T. SCHULTZ.

SPONTANEOUS HEALING OF MALIGNANT TUMORS. O. STRAUSS, Ztschr. f. Krebsforsch. **24**:367, 1927.

The author's study had as its basis the thought that spontaneous disappearance of clinically and histologically malignant neoplasms would be an important phenomenon if it could be shown to occur in even a fair percentage of cases. Study of such cases with the view of determining, if possible, the natural protective mechanisms might lead to methods of increasing resistance which would have therapeutic value. From the literature Strauss could collect only fifty-three examples which he was willing to accept as evidence of spontaneous disappearance or healing. This number he considers far too insignificant, among the hundreds of thousands of tumors which have occurred, to warrant any attempts at building up a resistance which the body does not appear to have naturally or to have in only slight measure.

O. T. SCHULTZ.

SUPRARENALECTOMY IN THE TREATMENT OF MALIGNANCY. H. FLÖRCKEN, Ztschr. f. Krebsforsch. **24**:465, 1927.

A number of more or less isolated hypotheses are united by the author into an idea which led him to believe that the removal of one surparenal might favorably influence the roentgen-ray therapy of malignant tumors. The suppositions accepted by the author as the basis of his procedure are that persons whose tumors do not yield to roentgen-ray irradiation are those who have a high blood pressure, hypertension being one of the conditions for which Stephan and Flörcken had previously practiced unilateral suprarenalectomy; that the reticulo-endothelial system is an important protective mechanism against cancer; that roentgen-ray irradiation acts not only by directly injuring the tumor tissue but also by stimulating the reticulo-endothelial system and that hyperfunction of the suprarenal cortex inhibits the protective activity of the reticulo-endothelial system. Unilateral suprarenalectomy was performed in twelve patients with inoperable tumors, the operation being followed by irradiation. Although all of the patients died, the author believes that the procedure was beneficial, in that some of the tumors decreased in size, some epithelialization of ulcerated tumors occurred and some of the patients increased in weight. In a series of mice with transplantable carcinomas, removal of one suprarenal followed by irradiation had no effect, but removal of both suprarenals, or of one and partial destruction of the other, slowed the growth of the tumors.

O. T. SCHULTZ.

ALBUMIN REACTION FOR THE DIAGNOSIS OF MALIGNANCY. F. P. TINOZZI, Ztschr. f. Krebsforsch. **24**:477, 1927.

H. Kahn, of Karlshruhe, applied the term albumin-A to a fraction of serum albumin which he claimed is more readily soluble and less easily precipitable than the rest of the albumin. It is not precipitated by *37.2* per cent ammonium sulphate,

and is coagulated by heat, properties which were made use of by Kahn in his reaction. Normal blood gives a recognizable cloud, whereas the blood of tumor hosts gives no precipitate or only a faint turbidity, such a result being termed positive. Tinozzi tried the reaction on the blood of 106 persons with malignant tumors, and obtained 68 per cent of positive results. The reaction was negative in 61 per cent of 119 patients free from tumor. These results the author interprets as indicating that the reaction is of value in the diagnosis of neoplasia.

O. T. SCHULTZ.

Medicolegal Pathology

BULLET FRACTURES OF THE CRANIUM. K. MEIXNER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **9**:1, 1927.

When the velocity of bullets is reduced, the force exerted on the cranium is disposed to produce fractures radiating out from the entrance hole, resembling those caused by blunt force. This does not occur with the higher velocities. The hole is clean-cut, as in panes of glass which have only a hole to mark the passage of a bullet travelling at great speed. Not only velocity, but also the size of the bullet, the distance of the weapon from the head and the degree to which expanding gases are also forced into the head determine the nature of the injuries sustained by the bones. With these factors so adjusted that the force resembles blunt force, the axes of the cranium for which entrance and exit wounds are the poles are shortened with the impact, and fracture may take place either with such shortening or with the rebound to normal shape. At wounds of exit the linear fractures leading away from the hole are often produced immediately after the bullet has passed through.

For all considerations with respect to hydrodynamics, the cranial content is to be regarded as a fluid with great resistance to pressure. Abruptly compressed by the bullet and perhaps by other substances entering with the bullet, such as fragments of bone, exploding ammunition and similar substances, it finds as its easiest outlet the holes made by the bullet, and the escape through them may be intermittent, owing to vibrations initiated by its compression and to vibratory return to a more nearly normal consistency. The momentarily greatly increased pressure is exerted by the cranial content in all directions and on all parts of the cranial wall. Where the wall is weakened by the bullet hole, fracture occurs when the conditions simulate those accompanying blunt force. Bullets with their force so spent that they merely flatten out against the innertable opposite the wound of entrance may exert a force there which makes the axis longer, the same axis which was shortened by the impact at the wound of entrance. These are examples of the matters discussed with many illustrations of bullet fractures of the cranium. Some of the illustrations used by Meixner may also be found in the eleventh edition of Hoffman's "Lehrbuch der gerichtliche Medizin," which has just been published.

Great care is urged that all the fragments be secured, for only by piecing them together and studying their location involvement of the outer and inner tables and extent is any comprehension of their significance possible. It may happen that a wound of entrance or exit will be found and its significance properly interpreted only by such care.

E. R. LECOUNT.

SUPRAVALVULAR SCLEROSIS OF THE AORTA. W. LAVES, Deutsche Ztschr. f. d. ges. gerichtl. Med. **9**:21, 1927.

Studies are still being made of supravalvular sclerosis of the aorta. It begins in the wall of the aorta about and just distal to the mutual attachments

of the three aortic leaflets, called the commissures. There are consequently three sites of origin, one, two or all of which may be diseased. The change consists of gray or slightly yellowish elevations with steep sharp edges, smooth on top or marked by shallow furrows separating trivial secondary elevations. The alteration spreads as narrow extensions around the root of the aorta and distally as far as the mouths of the large branches of the arch. Apparently these extensions toward the neck in the aortic wall develop after the horizontal spread around the root. They are referred to as "delta-like," and are more commonly from the commissures connected with that aortic leaflet which helps to form the sinus of Valsalva, where the left coronary artery has its mouth. Obviously, as the disease progresses circumferentially, the mouths of the coronary arteries are involved, and the thickening of the wall of the aorta at such places blocks the flow of blood into them, resulting in infarction of the myocardium and sudden death.

The relation of this type of aortitis to unexpected death has without doubt promoted interest in it. A controversy has occurred with regard to its origin; some consider trauma as its cause, others, including Laves, support an etiology in syphilis. It is said that the elastic fibers in the granulation tissue and in the scars which result from tears due to trauma possess a characteristic arrangement and that such a disposition is not found in this encircling supravalvular aortitis which radiates out from the commissures The highly cellular exudate in the media and advantitia, the location of this exudate chiefly about the nutrient arteries in the aortic wall and the minute necroses with peripheral giant cells resembling gummas, all indicate syphilis. Moreover, late stages with scarring have not been described, and this failure to progress to cicatrization is significant, for it constitutes a real similarity to the chronic inflammations to which many of the lesions of late syphilis belong, the infectious granulomas. Altogether plausible explanations for the commissural origin of the diseases have been suggested by the tug felt at such places with pulsatory dilation of the aortic root and the strain put on the valves and on the wall of the aorta where the ends of the free margins of the valves come together.

It will be recalled that just beneath the intima are bands of fibers arching up in the wall of the aorta from each commissure, like the spray from a fountain. These fibers extend higher than the distal margins of the sinuses of Valsalva and ultimately become buried in the media. Discussion of these bands has been concerned with their development, with the relation of their development to that of the aortic leaflets, whether they are simply remnants of the changes which result in the aortic leaflets and, finally, with their function as scaffolding-like supports for the aortic leaflets from the commissures well out into the ascending arch. It has been suggested that the location of this supravalvular aortitis is intimately connected with the presence of these extra bands of longitudinal fibers in the aortic walls, because the early lesions are triangular with one apex at the commissures, the opposite base the most distal part of the lesion and its margins parallel with the circumference of the aorta at that place.

It has also been assumed that these peculiarities of shape and location may be due to the influence of these arcades of fiber on the flow of lymph in the aortic wall during its pulsatory expansion and relaxation. Laves found but slight evidence of syphilis elsewhere in the body. In the eleven examples of supravalvular aortitis that he studied, microscopic changes resembling gummas were present in only one. He does not regard the absence of disease due to syphilis elsewhere in the body as a serious obstacle to accepting syphilis as the cause for this type of sclerosis, since many authorities, in commenting

on the changes in the knowledge of syphilis during the past decade, have emphasized the increased frequency with which the aorta presents the only changes when the disease has become chronic. E. R. LeCount.

Acute Poisoning with Potassium Bichromate. E. Jonsson, Hygiea **89**:84, 1927.

A man, aged 75, inadvertently and on a fasting stomach swallowed a quantity of a 5 per cent solution of potassium bichromate containing between 1 and 1.5 Gm. of potassium bichromate. After a short time, vomiting and diarrhea set in. The feces were of a green color and did not contain blood. Between six and seven hours later the patient developed painful convulsions of the arms and the legs. The heart function was regular, the pulse 90, but rose to 120 after defecation. The hemoglobin was 85 per cent, the erythrocytes numbered 4,780,000 and the leukocytes 6,400. Dyspnea and retention of the urine were present. The treatment consisted of administration of camphor and olive oil and intestinal lavage. The tonic convulsions of the legs were favorably influenced by subcutaneous injection of 500 cc. of sodium chloride. Two days after the poisoning, the patient was catheterized and 125 cc. of red-brown urine was obtained. The urine contained sugar, albumin, erythrocytes and leukocytes. The nonprotein nitrogen was 0.268 per cent. A few days later the diarrhea ceased and the secretion of urine became satisfactory. Venesection was twice performed and 150 cc. of blood was withdrawn on each occasion. After about six weeks the patient was discharged in normal condition, except for low blood pressure and cardiac arrhythmia.

Technical

Renal Glycosuria and Pentosuria. Harold W. Jones and Walker Sussman, Am. J. M. Sc. **173**:513, 1927.

Renal glycosuria and pentosuria are similar. Symptoms of diabetes do not occur in either condition; the blood sugar is normal. More than one member of the same family may be affected; pentosuria occurs most commonly in the Jewish race. Dextrose and pentose cannot be differentiated by means of the usual reduction tests. Differentiation may be made by means of Bial's test, by the special fermentation method of Castellani and Taylor, by estimating the melting point of the crystals, using the phenglhydrazin test, by Neumann's spectroscopic method and by estimating the nitrogen content of the crystals.

The Use of Hydraulic Devices for Obtaining Micromanipulation. F. Lowell Dunn, J. Infect. Dis. **40**:383, 1927.

Finely regulated movement can be obtained by using a system of two cylinders and pistons connected, and filled with a liquid, the ratio of movement varying inversely as the areas of the controlling piston and the driven piston. Hydraulic feed permits large variations in fineness of movement, design of apparatus and simple design of remote control with consequent great adaptability. When tested with a Michelson interferometer, vibration was scarcely seen and was less than a millionth of an inch in amplitude. Drift was not noted, and lag was barely perceptible, and the movement appeared as precise as the screw feed on the controlling piston. By avoiding accurately machined guides and highgrade screws as in the mechanical models, and utilizing hydraulic devices, fine movement can be obtained more cheaply and accurately.

Author's Summary.

PROTEINS OF THE CEREBROSPINAL FLUID. L. F. HEWITT, Brit. J. Exper. Path. **8**:84, 1927.

Concerning the colorimetric method—a modification of Wu's method of analysis of plasma proteins—of determining the proteins in the arachnoid fluid, reference is made to the original article. The normal fluid contains about 0.02 per cent of albumin and about 0.003 per cent of globulin, most of which is pseudoglobulin. In pathologic fluids both fractions are increased, but usually the globulin is more increased than the albumin.

BASAL METABOLISM AS DETERMINED BY THE RESPIRATORY EXCHANGE. F. A. PICKWORTH, Proc. Roy. Soc. **101B**:163, 1927.

The Douglas bag and spirometer methods for the determination of the basal metabolic rate are unsuitable for use with subjects suffering from mental disorders, as it is absolutely necessary, in an accurate measurement, to eliminate the disturbing factors of fear, anxiety and excitement. A new method is proposed which uses a specially constructed air-tight chamber in which the subject lies or sits for a period of one or two hours. The ensuing change in the composition of the atmosphere of the chamber is measured by a modified Haldane air-analysis apparatus. Metabolism is greatly decreased by trained, voluntary relaxation and by fatigue. It is increased by irritation or attention. The great increase produced by mental effort and during the period immediately following sleep may be partly due to an associated increase in muscular tone.

ARTHUR LOCKE.

SIMULTANEOUS DEMONSTRATION OF TUBERCLE BACILLI AND ELASTIC FIBERS IN THE SAME SLIDE. F. JESSEN, Beitr. z. Klin. d. Tuberk. **65**:4, 1926.

Four cubic centimeters of sputum is mixed with 10 cc. of a normal sodium hydroxide solution. The mixture is kept in a water bath at 50 C. for twenty minutes and is gently stirred with a glass rod; then it is centrifugalized and the sediment spread over a slide as usual. After drying, it is fixed in the flame, stained with carbol-fuchsin, decolorized with 3 per cent hydrochloric acid in alcohol, as usual, and counterstained for from one to two minutes with the following mixture:

	cc.
Hematoxylin saturated solution	1
Lithium carbonate saturated solution	1
Absolute alcohol	10
Distilled water	10

The stain is rinsed off with water and then the smear is treated for a few seconds with a 28 per cent solution of ferric chloride. The tubercle bacilli are red; the elastic fibers blue-gray.

MAX PINNER.

THE USE OF DRIED COMPLEMENT IN THE WASSERMANN REACTION. PETER O. GANZ, Centralbl. f. Bakteriol **101**:225, 1927.

Ganz describes the use of a dried complement prepared by a pharmaceutical house. In 860 tests it was as specific and sensitive in the Wassermann reaction as fresh complement. The use of this dried complement saves much time, makes one independent of epizootics among guinea-pigs and is especially convenient for mobile laboratories. It also contributes to the standardization of the Wassermann reaction.

PAUL R. CANNON.

AGAR AS AN INCLUSION MEDIUM FOR DARK-FIELD WORK. TOHL SHMAMINE, Centralbl. f. Bakteriol. **101**:279, 1927.

The use of a 3 per cent nutrient agar in which material may be mixed while the agar is melted and then hardened under the coverslip offers many advantages for dark-field studies, especially for the finer structure, the growth and death of organisms.

PAUL R. CANNON.

STERILIZATION AND CONSERVATION OF ASCITIC FLUID FOR CULTURE MEDIUMS. B. BUSSON, Centralbl. f. Bakteriol. **101**:282, 1927.

Busson states that the use of from 5 to 10 per cent solution of potassium or sodium hydroxide in sufficient amount to make the final concentration of the ascitic fluid approximately 0.5 per cent alkali, sterilizes ascitic fluids even when they are badly contaminated. For use, 100 cc. of this fluid is then titrated to neutrality with phosphoric acid. This amount of phosphoric acid is then put into small sterile flasks and used with the ascites fluid as needed.

PAUL R. CANNON.

A SIMPLE MEANS OF CONSERVING BACTERIAL CULTURES. BRUNO DIKOMEIT, Centralbl. f. Bakteriol. **101**:290, 1927.

Dikomeit has used Nizles' medium which consists of equal parts of wool fat and liquid paraffin, to test the survival time for various pathogenic organisms. He finds that streptococci may live unchanged in properties for one year, pneumococci for six months, meningococci for one month and diphtheria, typhoid and dysentery bacilli at least for seven and one-half months.

PAUL R. CANNON.

HISTOLOGIC DETERMINATION OF CARCINOMA AND TUBERCULOSIS FROM PARACENTESIS MATERIAL. H. MÜLLER, Klin. Wchnschr. **6**:116, 1927.

Subphrenic puncture with an aspirating needle yielded pinhead-sized tissue particles which were histologically prepared in the usual way. Diagnoses of carcinoma and tuberculosis were made and substantiated by abdominal section or autopsy.

J. D. WILLEMS.

DEALBUMINATION OF URINE. I. ABELIN, München. Med. Wchnschr. **73**:2066, 1926.

One drop of phenolsulphonphthalein solution is added to 40 cc. of a tenth-normal solution of sodium hydroxide, and a 10 per cent solution of zinc sulphate is added drop by drop until the red color disappears. The quantity is now brought up to 50 cc. by adding water, 50 cc. of urine is added, and the mixture is placed for five minutes in a boiling water bath and then filtered. The filtrate is free from proteins and can be used for quantitative determinations of other urinary constituents. Two cubic centimeters equals 1 cc. of urine.

THE VOLUME DETERMINATION OF THE THROMBOCYTES. C. M. VANALLEN, München. med. Wchnschr. **74**:141, 1927.

A known quantity of blood is mixed with an isotonic sodium oxalate solution and placed in a special sedimentation chamber. The blood platelets settle out, and are placed in a special thrombocytocrit and centrifugalized. Their volume is read off directly on a percentage scale.

J. D. WILLEMS.

Society Transactions

AMERICAN ASSOCIATION OF IMMUNOLOGISTS

14th Annual Meeting, Rochester, New York, April 14 and 15, 1927

LUDVIG HEKTOEN, *President;* A. F. COCA, *Secretary*

OBSERVATIONS ON PRECIPITIN REACTION. LUDVIG HEKTOEN.

The results of observations on the precipitin reactions of certain normal constituents of the animal body were discussed. Of the substances considered, the serum proteins, hemoglobin and the specific precipitinogen in semen appear to be distinctive or specific for the species, and consequently are presumably different chemically in each species, while the lens proteins, fibrinogen and thyroglobulin appear to be more or less closely related in many distinct species. Of the latter group, the lens and casein have been the standard illustrations, and now fibrinogen and thyroglobulin can be added. That fibrinogen should disregard so completely the species limitations of the immune reactions of serum and its constituents, as well as the reactions of hemoglobin, is both surprising and interesting. In fibrinogen the blood reveals a much wider antigenic relationship than is ordinarily assumed to be the case. It is of special interest in connection with the fundamental problems of immune specificness and the production of antibodies that these non-species-specific antigens can evoke the formation of corresponding antibodies in the homologous species, at least under certain conditions.

SEROLOGIC ASPECTS OF THE DISSOCIATION OF BACILLUS SUBTILIS. M. H. SOULE.

From cultures of *B. subtilis*, some of which were from single cell isolations, at least three types of organisms were isolated: the normal or S form, equivalent to that first described by Ehrenberg and later by Cohn, Koch and others; an R or resistant form which varied morphologically and culturally from the classical type, and a P or intermediate form which has not been reported previously.

The S is an unstable form, and in fluid mediums it shows a marked tendency to dissociate into R forms. The R type is stable; + serial cultivations through 400 generations in 5 cc. quantities of broth failed to produce any other types. The P form was obtained from rapidly dissociating cultures, and was stable only on solid mediums. All attempts to obtain broth cultures of this type were unsuccessful; on dissociation it gave the R form.

Antiserums for the three types were developed in rabbits by the intravenous injections of live germs. In several experiments the antigens were attenuated at various temperatures, but suspensions incubated at 80 C. for one hour exhibited no change in antigenic properties. The S form is the "strongest" antigen.

The S serum agglutinated the S organisms in titer of 1:2,560, and the R microbe to a dilution of 1:640. The R serum agglutinated both the R and S germs in titer of 1:640. The P serum agglutinated both the R and S germs in titer of 1:200. S organisms absorbed both the S and R agglutinins from S serum, and the S agglutinins from both the R and P serums. The R germs

absorbed a small amount of agglutinins from the S serum, and only the R agglutinins from both the R and P serum.

Immune serum has a marked dissociating power on its homologous germs and a stabilizing action on the opposite form. By the incorporation of S or R immune serums in fluid mediums, R forms can be obtained from S forms and S from R, respectively. The P type can be isolated from cultures of the R or S type which are undergoing rapid dissociation in the presence of immune serums.

THE BACTERIOPHAGE-ANTIBACTERIOPHAGE REACTION. EMIL WEISS.

The experiments described are a continuation of the study of antigenic properties of phage. Evidence has been submitted showing the following points: 1. Antilysins are the only antibodies produced by bacteriophage. 2. The law of multiple proportions is operative. 3. Inactivated (heated) phage possesses antigenic properties and unites with antiphage. 4. Time and temperature have a similar influence on the union of phage and antiphage. 5. The Bordet-Danysz phenomenon in both instances is positive. 6. The Berkefeld filtrates of mixtures of phage and antiphage do not exert lytic activity.

In addition other observations have been made. 1. The colloidal sac filtrates behave the same as the Berkefeld filtrates. 2. Phage mixed with antiphage does not penetrate an average agar layer in a Petri dish, but penetrates when alone or mixed with normal serum. 3. Phage mixed with antiphage is precipitated with 13.5 per cent sodium sulphate, but remains in the filtrate when mixed with normal serum or alone. 4. Phage is not destroyed by its union with antiphage serum, as shown by tryptic digestion.

These results justify the placing of phage in the same group with toxins and ferments; for the same reason, the reaction between phage and antiphage cannot be interpreted otherwise than as a neutralization.

THE QUANTITATIVE RELATIONSHIP OF CULTURE AND ANTIBODY WITH REFERENCE TO THE STANDARDIZATION OF ANTIPNEUMOCOCCUS SERUM. GEORGIA COOPER.

The quantities of serum and culture usually employed in protection tests to determine the value of antipneumococcus serum were found to be open to criticism. The methods in use generally include in the titration for potency, the test of comparatively large amounts of antiserum against a concentrated dose of culture. Experiments show that large amounts of antiserum often fail to protect against large doses of culture, while smaller amounts of antiserum protect. This is termed a zone of inhibition of protection. This zone tends to be greatest with type III, less extensive with type II and least or often absent with type I.

Titrations of antiserum with different doses of culture showed that when this zone of inhibition of protection did not enter as a factor, the amounts of antiserum protecting against large doses of culture, that is, those containing from 100,000 to 50,000,000 fatal doses followed roughly the law of multiple proportions. With smaller amounts of culture, it was evident that a definite minimum amount of antiserum was required to secure protection. Equal amounts of antiserum or amounts close together protected against 10,000, 1,000 and 100 fatal doses. Sometimes less than this would protect against 10 fatal doses.

This work in general agrees with that of Neufeld and Handel (*Ztschr. f. Immunitätsforsch.* **3**:159, 1909), but is in disagreement with the work of Avery,

Chickering, Cole and Dochez (Monograph 7, Rockefeller Institute, 1917). The latter workers found that protection followed the law of multiple proportions.

It seems desirable to find a dose of culture which may be used with all three types of antiserum. It is believed that the most consistent results may be obtained by titrating the antiserum with an amount of culture containing approximately 100,000 fatal doses; in this work this strength was usually contained in 0.001 cc. of an eighteen-hour culture. As it is desirable that a uniform method for testing be utilized by all, it is suggested that a committee take this matter under consideration.

DISCUSSION

I. S. FALK: I should like to refer to a few points of interest that are suggested by Dr. Cooper's paper. First, it should be recalled, as my colleague Dr. Taliaferro has recently done in a paper in the *Journal of Preventive Medicine*, that, from an historical point of view, the observation of zonal phenomena in vivo preceded similar observations by Neisser and Wechsberg in studies in vitro. Pfeiffer, among others, reported such observations. Second, what is more consequential, Dr. Taliaferro has reported that in experiments with trypanosomes, recurring zones of inhibition are demonstrable. Furthermore, in a paper which is to appear shortly in the *American Journal of Hygiene*, Dr. Coventry, of our laboratory, reports recurrent zones of lysis in experiments with pneumococci. Instead of the single zones described by Dr. Cooper, there are probably many zones, and these may not be of fixed position. Third, it is important to recall that neither in Dr. Cooper's work nor in other similar studies on the standardization of antipneumococcus serum is due regard given to the importance of a point of technic — the significance that attaches to the simultaneous administration of culture and serum. Accordingly as serum is given before, simultaneously with, or after the culture, the standardization is different. And, finally, I wish to present my emphatic objections to Dr. Cooper's suggestion that the problems in serum standardization which she raises should be referred to a committee. A committee cannot settle such problems until an adequate body of facts has been obtained. These are not matters for arbitration, but for investigation.

JOSEPH D. ARONSON: A prezone has been noted frequently in precipitin reactions carried out with serum of goats infected with virulent cultures of bovine tubercle bacilli, using old tuberculin or watery extracts of tubercle bacilli as antigen. Similar observations with reference to the opsonic index have been observed with serums of goats immunized with an avirulent strain of bovine tubercle bacillus.

THE ETIOLOGY OF MEASLES. R. DEGKWITZ.

1. The organism causing measles can be kept alive for several weeks outside the human system if blood is drawn from patients with measles just at the beginning of the rash and diluted in the proportion of 1:7 and 1:10 with a buffered solution of physiologic sodium chloride containing the same amount of anions and cations and showing the same p_H as living blood. This mixture has to be kept at a temperature of 0 C.

2. Measles following an infection of the skin comes sooner than spontaneous measles or measles following an artificial infection of the mucous membranes of the respiratory tract. There seems to be a morbillization against measles as there is variolation against smallpox.

3. Measles can be reproduced in man with material which is sterile from a bacteriologic point of view, with originally sterile blood of a measles patient

drawn at the right time or with dilutions of such blood which have passed through a Berkefeld filter. Sterile filtrates of nasal secretions collected in the pre-eruptive state of the disease and diluted with physiologic sodium chloride are also capable of reproducing measles.

4. Measles virus can be grown in vitro in culture mediums containing plasma of susceptible persons, which is diluted in a proportion of 1:6 or 1:7, with buffered physiologic sodium chloride. In order to keep the virus alive and to secure growth, it is necessary to associate it with living cells, such as living human cells or slowly growing bacteria regularly found in cases of measles.

5. With sterile filtrates reactions can be caused in man which are similar to measles, the specificity of which can be proved by the fact that such persons are immune against large amounts of originally infectious material.

6. Monkeys (M. Rhesus) can be made sick by injections of such material, and the specificity of the reactions can be proved by the fact that their serum collected after the reaction is able to protect infected human beings against measles, while normal monkey serum will not do so.

HEMOLYTIC STREPTOCOCCI IN SCARLET FEVER AND ERYSIPELAS (SEROLOGIC RELATIONSHIPS). ANNA W. WILLIAMS, CAROLINE R. GURLEY ET AL.

More than 300 case strains of hemolytic streptococci from scarlatina, erysipelas and other sources have been studied in whole or in part as to their serologic relationships. A more intensive comparative study has been made of about 100 of these strains, the results from which are summarized in the attached table and diagram.

Relationship of Strains of Hemolytic Streptococci to Carbohydrate Reactions and Agglutinin Absorption

							Typed by Agglutinin Absorption							
							I [2]		II	III	Scarlatina IV	Erysipelas I		
Source	Number of Cases	Lactose	Mannitol	Salicin	Inulin	Holman's Types	G I	Sub I 55[4]	G II	57[3]	28[1]	Birkhaug C[5]	Birkhaug B[3]	Unclassified
Scarlatina	58	+	—	+	—	Pyogenes	4	32	1	..	14	..		6
Scarlatina	7	+	—	—	—	Anginosus	..	..	..	7	..	..		..
Scarlatina	8	+	+	+	—	Infrequens	..	..	..	..	..	..		3
Erysipelas	12	+	—	+	—	Pyogenes	..	..	..	..	10	..		2
Erysipelas	3	—	—	—	—	Subacidus	..	..	..	..	..	3		..
Other sources	10	+	—	+	—	Pyogenes	1	3	..	..	1	..		..

Some strains have given evidence of splitting into coarse and fine (rough and smooth) colonies, subcultures from which may give agglutinative reactions differing from that of the original strain. This phenomenon could explain at least some of the irregularities reported in studies of this group of bacteria.

The table and the diagram show the following results:

Strains of hemolytic streptococci have been obtained from cases of scarlatina. Most of these strains, by absorption of agglutinins, fall into one of three groups and one subgroup.

Accepting Griffith's type I and type II as distinct agglutinative groups we describe four agglutinative types and one subtype. Type I is the same as Griffith's type I. Our type strain is 2 (2). Only three strains of ours fell into this group. Including Griffith's type strain, we have four strains from scarlatina and one from mastoiditis in this group. It is dominant over most of our strains.

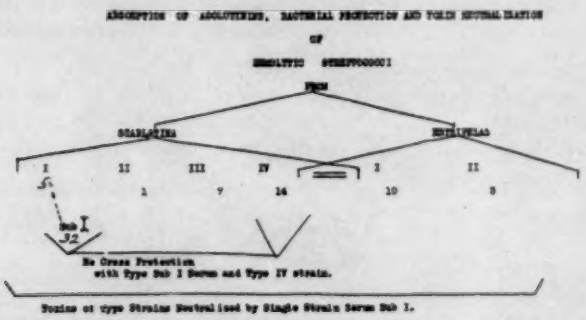
Type sub. I: Our type strain is 55.[4] Most of our strains — thirty-two in number — fall in this group. As Griffith says that our 55[4] falls in his type III group, his type III must be considered type sub. I. The strains sent to us by Dochez and the Dicks belong here.

Type II: Working with Griffith's type strain, we have found no strain in New York City that falls into this group.

Type III: All of our seven scarlatinal strains that belong to anginosus (Holman's classification) by carbohydrate fermentation are of this type by absorption of agglutinins; 57[2] is the type strain of this group.

Type IV: A comparatively large group of strains — fourteen are of this type. The most important fact concerning this group is that its members cross absorb with strains of group I, from erysipelas. The type strain is 28.[1]

Strains of hemolytic streptococci from erysipelas fall into one large group, type I; a small group, type II, and a few heterogeneous strains. Most of Birkhaug's strains fall into the larger group. The three strains of type II belong to the subacidus group by carbohydrate fermentation.



Serologic relationship of hemolytic streptococci from scarlatina and erysipelas.

Strains from all of these groups, both from scarlatina and from erysipelas, produce a toxin that may be neutralized in some human beings by both scarlatinal convalescent serum and by our subtype I antitoxic horse serum.

A subtype I horse antiserum which is strongly protective against the subtype I strains does not protect against the type strain 28[1] of type IV group.

Conclusion.—Scarlet rash is merely a symptom produced by the toxins of a large group of hemolytic streptococci, certain members of which may cause erysipelas. These members, while producing toxins similar to those of the majority of strains from scarlatina, may stimulate the production of an antiserum different from that produced by strains belonging to other types. Erysipelas, therefore, may require a special antibacterial serum, while any type of scarlatinal antitoxic serum may combat the exotoxins in at least certain cases of this disease.

DISCUSSION

K. E. Birkhaug: It is a matter of great concern to me to know whether or not the blood-serum of rabbits to be immunized against individual strains of streptococci contains natural agglutinins for the streptococci I am planning to employ for specific agglutination and absorption. In my earliest paper on the biology of *Streptococcus erysipelatis,* I pointed out that of the stock rabbits,

about 25 per cent possessed natural agglutinins for the group of streptococci I was anxious to employ, and that all such animals were consequently discarded. I am sorry to learn that this logical procedure is not observed, and hence all the confusion has arisen about the inability of certain workers to find specific groupings of *Streptococcus scarlatinae* and *Streptococcus erysipelatis*. In a recent lot of stock rabbits tested for natural agglutinins for scarlet fever and erysipelas streptococci, it was found that 60 per cent of the rabbits possessed natural agglutinins for both groups of streptococci, the titer running as high as 1:10,240, the agglutinins being subsequently removed completely by reciprocal absorption with the *Streptococcus scarlatinae* (Dick I, IIS, III; Dochez NY5; Birkhaug 218, 268, 323) and the *Streptococcus erysipelatis* (Birkhaug E-I, E-2, E-4, E-6). In carefully controlled agglutination studies with scarlatinal and erysipelatis streptotococci, observing particular care in the isolation of the respective streptococci from typical clinical cases of scarlatina and erysipelas, I have consistently failed to corroborate the observations of certain workers who claim an extensive overlapping of scarlatinal antiserums with *Streptococcus erysipelatis* and vice versa. The average agglutinin titer of my *Streptococcus erysipelatis* antiserums has been 1:5,120 when tested with homologous streptococci. When these serums were employed with true *Streptococcus scarlatinae*, agglutinations were obtained in dilutions of 1:20 and on only a few occasions as high as 1:160. Absorption tests further demonstrated a marked specificity within the groups of *Streptococcus scarlatinae* and *Streptococcus erysipelatis*.

As regards the ability of scarlatinal antitoxin to neutralize completely the soluble toxin produced by the *Streptococcus erysipelatis* and vice versa, most certainly such neutralizations are possible when a large quantity of antitoxin is employed. When careful quantitative determinations are carried out for the estimation of antitoxin units contained in each cubic centimeter against the soluble toxins produced by the scarlatinal and erysipelatous streptococci, the specificity of the *Streptococcus erysipelatis* antitoxin to neutralize completely the soluble toxin of the *Streptococcus erysipelatis* is apparent. For example, 1 cc. of the antitoxin is able to neutralize 50,000 skin test doses of the toxin. When the Dick toxin is placed against the erysipelas antitoxin, then 1 cc. of the latter is able to neutralize completely about 500 skin test doses of the Dick toxin. For that matter, Rivers and Tillett have demonstrated that ordinary broth will exert a slightly inhibitory effect on the pathogenic power of *Streptococcus erysipelatis*, when the broth is injected intradermally twenty-four hours previous to the injection of the living and virulent streptococci.

If it were true, as some workers have said, that no difference exists between the toxins produced by the scarlatinal and erysipelatous streptococci and that the antitoxin produced by the one streptococcus will neutralize the toxin produced by the other organism, it seems to me most curious that the two clinical pictures should be so dissimilar. One presents a generalized erythema and the other a localized infectious process which presents microscopic changes unique for erysipelas. Again it is strange that an attack of scarlet fever should bestow on the patient permanent immunity and that erysipelas should leave the patient with an increased susceptibility to repeated attacks of the disease. The difference between the soluble toxins produced by *Streptococcus scarlatinae* and the *Streptococcus erysipelatis* was clearly demonstrated when, among 408 persons tested intradermally with one skin test dose of both toxins simultaneously, 52 per cent gave positive reactions with the Dick toxin, 24 per cent reacted positively with the erysipelas toxin and only 10 per cent

of this group gave simultaneously positive reactions with both toxins. I still maintain that when pure strains of the scarlatinal and erysipelas streptococci are studied biologically, a specific difference between these two types is apparent.

SPECIFICITY OF RAMON FLOCCULATION TEST IN SCARLET FEVER. OLGA R. POVITZKY.

The first paper on this subject was presented to the Soc. of Exper. Biol. & Med., May, 1925. The work was continued, and special experiments with different controls established the efficacy of this test for the determination of the potency of scarlet fever toxins and antitoxins. Bleedings of horses injected with scarlet fever toxin were tested each month, and the results, when comparison was possible, usually agreed with those of intracutaneous neutralization tests in children. The curve of the progress of the immunization of the horses with scarlet fever with its gradual rise, fluctuations and drops could thus be studied as efficiently as in the case of horses with diphtheria. Control experiments for the specificity of this test with normal serum, broth, diphtheria toxins and antitoxins, also antibacterial streptococcus and pneumococcus serums were repeated, and the negative results obtained before were confirmed. The most important control, however, was the 1 per cent sheep's blood pneumococcus broth used for the growth of the scarlet fever toxin, and incubated at the same time as the toxin. This blood control gave reactions not only with scarlet fever antitoxins, but also with diphtheria antitoxins, antipneumococcus and antibacterial streptococcus serums. That these were pseudoreactions, due to the sheep blood and fortunately not manifested in the presence of the scarlet fever toxin (due probably to the modification of the blood and change of the p_H reaction by the growth of the scarlet fever *Streptococcus hemolyticus* in the broth) was proved by the following results: 1. The reactions with the control blood broth appeared in all tubes at the time when there was not even a trace of a reaction with the mixtures containing scarlet fever toxin-antitoxin in the early period of the immunization of the horse. 2. When the reaction between the toxin and antitoxin occurred, it showed only in the neutralization zone, for example, the tubes with a great excess or deficiency of serum remained clear, while the reactions with the control appeared in each tube, irrespective of the amount of serum. 3. The pseudoreactions usually occurred in the form of a film, which could be removed before shaking up.

The following points were found to be essential for the successful result of the test: 1. A toxin standardized for the number of toxic skin doses by the Dick test in children. 2. As a preservative, phenol, preferably the crystals, in 0.3 per cent solution is used. The ingredients, toxin as well as antitoxin, should be perfectly clear for the test. If they are not clear after centrifugalization they are passed through sterile filter paper. 3. A constant amount of toxin and varying amounts of serum are used for the test. For weak serum the toxin is used in 0.5 cc. and for stronger serum in amounts of 1 cc. per tube. It is preferable to use large amounts of weak serum, rather than dilute the toxin even slightly. This is true in principle of every Ramon test. 4. The optimum temperature for the scarlet fever test is 37 C.; anything above this point was found to inhibit the reaction. 5. The first reactions to appear in the test tube were found to correspond to those in the intracutaneous neutralization tests in children. 6. The reactions usually appear in from twelve to eighteen hours. With some serums it may be twenty-four hours or even forty-eight hours, especially in case of concentrated serum. Here also, as in diphtheria, the serums of certain horses preserve their characteristics as to the slowness

or rapidity of their flocculation reactions. If, for instance, no flocculation is shown within eighteen hours in a case of a serum which previously has shown reactions within that time, it is probable that the proportion between the toxin and antitoxin is wrong, and the test should be made over, instead of waiting for a possible later reaction.

The agglutinin content of four representative scarlet fever horses was studied, because the results may have some bearing on the nature of toxin-antitoxin flocculation. Horses A and C had 85 toxin inoculations, 52 injections of killed cultures and 4 Dochez treatments. Horses 140 and 141 had 26 and 45 inoculations by the Dochez method, respectively. Horse C, which had the lowest antitoxin content by the Ramon test, showed the highest agglutinin titer (1:3,200, higher not tried). Horse A showed agglutination in 1:400, though the antitoxin content by the flocculation test was higher than that of the previous horse. Horses 140 and 141, on the other hand, showed the highest antitoxin content by the Ramon test, and at the same time did not give any agglutination in any dilution with the same bacterial antigen. These results would seem to indicate that the antitoxin content of the serum as manifested by the Ramon test is not dependent on the bacterial content of the serum for the reaction, contrary to the view propounded by Bronfenbrenner and Reichert in their work on "The Nature of the Toxin-Antitoxin Phenomenon." Whatever the nature of the Ramon flocculation may be, the immediate object is to obtain a reaction between toxin and antitoxin for the purpose of determining the potency of one or the other. Substitution of an atoxic filtrate for toxin or of an antibacterial antigen for antitoxin as done by Bronfenbrenner and Reichert to prove their contention, does not constitute the Ramon test; it merely produces the inevitable bacterial precipitation reactions. These reactions, though useful for the determination of antigen-antibody content, are of no value for the quantitative determination of either toxin or antitoxin. Failure to obtain results by the Ramon test may be attributable to improper technic, such as dilution of toxin, too small amounts in the test tube for a clear-cut reaction, unsuitable temperature and, last but not least, wrong proportions between toxin and antitoxin.

ANAPHYLAXIS IN THE RABBIT. ELLA F. GROVE.

The previous investigators of anaphylaxis in the rabbit have reported irregularity in the production of a fatal degree of hypersensitiveness in this animal.

After the treatment to be described the first series of five animals all died within five minutes after intravenous injection of the antigen white of egg. In the three subsequent series, in which horse serum or white of egg was used, the precipitin content of the blood was followed, and the final test of hypersensitiveness was made only in those animals (the majority) which presented a low precipitin production. These animals all died on intravenous injection of the antigen within from five to ten minutes, and the pulmonary vessels withstood a water pressure of about 90 cm. in the only one of them that was tested in this way. The precipitin titer (ring technic) in these rabbits ranged between 1:10 and 1:100.

Two rabbits of these series received subcutaneous injections of 2 or 3 cc. of the antigen, but did not develop the local necrosis of Arthus. The precipitin titer of the serum of these two animals was respectively 1:10 and 1:80,000. A relation between the general and the local hypersensitiveness in the rabbit or between precipitin production and the local hypersensitiveness is not apparent in these results.

The treatment employed was: first day, 0.5 cc. intravenously; sixth day, 5 cc. intraperitoneally; from the eleventh to the eighteenth day, daily, 1 to 2 cc. intraperitoneally; twenty-fourth day, 1.5 cc. subcutaneously; from the thirtieth to the thirty-sixth day, test by intravenous injection of antigen. Many rabbits under this treatment are found to be not sensitive on the twenty-fourth day.

The experiments of Airila and others provide evidence that the general anaphylactic shock in the rabbit is due to a contraction of the arterial mediums in the pulmonary circulation. Manwaring has recently questioned this explanation, because the contraction of the bladder, which he observed in anaphylactic shock in the guinea-pig, was lacking in the sensitized rabbits; this observation indicates, according to Manwaring, that unstriped muscle takes no part in anaphylactic shock in the rabbit.

This phenomenon was studied first by testing the bladder muscle of highly sensitized guinea-pigs in the Dale bath. The muscle was insensitive to the antigen, but contracted vigorously on addition of histamine. The nonspecificity of the bladder phenomenon in the guinea-pig described by Manwaring was then demonstrated by ligating the trachea of normal guinea-pigs. In all cases, the bladder contracted vigorously in from one to two minutes after the ligation.

The following papers were presented in a joint session with the Association of American Pathologists and Bacteriologists:

THE ABSORPTION OF THE TOXIC SUBSTANCE OF NORMAL GOAT SERUM BY GUINEA-PIG TISSUE. JOSEPH D. ARONSON.

Fresh normal goat serum produces necrosis when injected into the dermis or into the subcutaneous tissue of normal guinea-pigs. When it is injected directly into the general circulation or into the periteoneal cavity, death results. Furthermore, the addition of fresh normal goat serum to washed guinea-pig cells lakes these cells. It seemed likely that these differences in the results obtained from injecting the serum into different parts might depend on the fixation of the serum by the different tissues. Experiments were undertaken to determine whether a selective absorption by the different tissues existed for the hemolysin, necrotizing substance and toxic substance of normal goat serum.

The organs of normal guinea-pigs were ground in a mortar with physiologic sodium chloride, filtered through gauze and washed. To varying amounts of the washed tissue cells was added 2 cc. of fresh, unheated goat serum, and the mixture of cells and serum was shaken for two hours at 37 C. After centrifugalizing, the supernatant serum was collected and tested for its hemolytic action on guinea-pig cells and for its necrotizing and toxic action on guinea-pigs.

It was found that while the suprarenal, heart, voluntary muscle and spleen did not absorb the hemolytic or necrotizing substance, the liver, kidney, skin, testes and erythrocyte stroma absorbed this substance. The brain and lungs showed some diminution of the hemolytic action and removed completely the necrotizing effect. The toxic substance was absorbed by suspensions of kidney, liver and testes, but not by the spleen.

When the suspensions of the different guinea-pig tissues are heated at 70 C. or higher for thirty minutes or are heated at 100 C. for ten minutes, their ability to absorb the goat serum hemolysin and necrotizing substance is decreased or destroyed completely.

It was found that erythrocytes of rats and mice were relatively resistant to the lytic action of normal goat serum and that these animals were insusceptible to the necrotizing and toxic action of normal goat serum. Suspen-

sions of the spleen, brain, liver, kidneys and testes of rats prepared in the same manner as those from guinea-pigs were unable to absorb the hemolysin present in normal goat serum.

The fixation of the hemolysin to the kidney or liver cells is firm, and the hemolysin could not be dissociated from the cell by extracting with physiologic sodium chloride, distilled water, 0.1 per cent sodium carbonate or by freezing and thawing.

LOCAL HYPERSENSITIVENESS. L. DIENES.

Tuberculous guinea-pigs injected with white of egg (from 0.3 to 50 mg.) give, five or six days later, a large evanescent reaction in the skin to the intracutaneous injection of 0.1 mg. of white of egg. From the seventh or eighth day after the injection they respond during several weeks with a strong necrotic reaction, and after some weeks the evanescent reaction reappears. The reactions in the skin begin to appear in from fifteen to twenty minutes after the test injections. The guinea-pigs cannot be killed with the subcutaneous injection of white of egg, but they develop a typical Arthus phenomenon. The blood serum usually gives strong precipitation, and in many cases complement fixation in high dilution. Passive transfer of the sensitiveness with blood serum is possible, but only the evanescent large reactions are obtained in the passively sensitized animals. The sensitization of the tuberculous guinea-pigs was not so successful during the winter as in the summer and fall.

For the evaluation of the importance of the differences which are present between the reactions to white of egg and to tuberculin, certain details of the observations are important. Four guinea-pigs treated with white of egg showed only slight precipitins. Two of the four gave strong necrotic reactions in the skin. On the other hand, tuberculous guinea-pigs treated with small amounts of a watery extract of tubercle bacilli show a large amount of precipitins in the serum, and with the serum of such animals the passive transfer of the sensitiveness to tuberculin is possible. The passively transfered sensitiveness to tuberculin is in all characteristics similar to the passively transferred sensitiveness to white of egg. Too little is known of the physiologic mechanism, of the sensitiveness to both white of egg and tuberculin to enable one to decide whether the two reactions are essentially similar, but the differences between them are not of such a nature that they would exclude an essential similarity.

The development of strong local hypersensitiveness and abundant production of antibodies in the tuberculous guinea-pigs by the injection of small amounts of white of egg emphasizes the importance of the observations of Lewis and Loomis on the increased antigenic response of tuberculous guinea-pigs. If a similar increase of response is present also in other infectious diseases, it must be an important factor of the mechanism of immunity. Observations previously made by Dr. Dienes in typhus fever indicate that an increased antibody formation is probably present in certain phases of the course of this disease.

STUDIES ON THE ABSORPTION OF UNALTERED PROTEIN. MATTHEW WALZER.

A direct method of demonstrating and studying the absorption of undigested protein in man is presented. It is based on the principle of passive local sensitization. About 0.05 cc. of the serum taken from certain asthmatic patients who are markedly sensitive to fish or egg, was injected intradermally

into normal persons. Following an eight-hour fast, white of one egg or 50 Gm. of raw herring was ingested. Within from three minutes to two and one-half hours, a wheal usually developed at the sensitized site, as a result of the absorption into the cirulation of some of the protein in an undigested state. The reaction was proven to be specific.

Of sixty-five adults tested with fish protein, 93.8 per cent demonstrated the phenomenon (Brunner and Walzer); of thirty-four adults tested with egg protein, 85.3 per cent reacted (Sussman, Davidson and Walzer), as did also 71.8 per cent of sixty-four children, from 1 to 4 years of age (Wilson and Walzer). Four infants, 1 week old, tested with egg, demonstrated the phenomenon. Absorption of unaltered egg protein from the rectum occurred in four out of five adults tested. Most reactions to fish occurred during the first thirty minutes, while most reactions to egg occurred in the second half hour. Intradermal tests done with the sensitive serum after the protein was eaten resulted in a series of positive specific reactions in the skin, for a period of at least twelve hours, the strongest occurring between the third and the sixth hour when the protein was at its height in the circulation. From these facts, it may be concluded that the absorption of undigested protein is a normal and physiologic phenomenon in man.

Dermal Testing as an Aid to Diagnosis of Intestinal Parasitic Infestation. Matthew Brunner.

Saline extracts of *Ascaris lumbricoides, Dibothriocephalus latus* and *Taenia solium* were made. Intradermal tests with these extracts in various dilutions were made on 270 persons. Reactions similar to those elicited in conditions of atopic hypersensitiveness (hay-fever, asthma and other conditions) were obtained. In 148 positive reactions, 20 of 143 stools were positive for ova and parasites. Of 399 negative reactions, 1 stool was found positive for ova and parasites.

A marked or moderate reaction has been found to indicate either the presence of parasites or a previous infestation. The absence of a positive reaction is not an absolute criterion of an absence of infestation; one infected person gave negative reactions to repeated tests. The dermal test is useful in encouraging a more persistent search for infestation.

Those reacting to *Ascaris* extract were infested with *Ascaris lumbricoides, Trichiuris trichiuris, Oxyuris vermicularis, Uncinariasis americana, Trichinella spiralis,* indicating a group reaction for the *Nematode* family.

A positive reaction with *Dibothriocephalus* extract revealed the *Dibothriocephalus* infestation, and *Taenia solium* extract *Taenia solium* tapeworm.

In every positive reacting case in which passive transfer to the human skin (method of Prausnitz and Küstner) was undertaken, the transfer was successful, even in persons in whom an active infestation could not be demonstrated.

Constitutional symptoms (asthma) were induced in the course of dermal testing in three persons, all of whom were subject to asthma.

A Comparative Study of Basic Beef Heart Antigens in the Wassermann Test. Marjorie C. Albray and L. W. Famulener.

Three series of antigens were studied in duplicate with and without the addition of cholesterol. In no case was the efficiency of the antigen increased by cholesterol.

STUDIES OF ATTENUATION AND OF TOXIN PRODUCTION OF THE DIPHTHERIA BACILLUS. MARY W. WHEELER.

Toxin can be produced by growing diphtheria bacilli in solutions of peptone, dextrose and salts without the addition of meat infusion. Rehabilitation of attenuated strains was not successful.

ACTIVE IMMUNIZATION AGAINST EXPERIMENTAL PERITONITIS. BERNHARD STEINBERG and HARRY GOLDBLATT.

Death from general peritonitis can be prevented in dogs in which feces have been smeared throughout the peritoneal cavity provided the dogs are first immunized by injecting a suspension of *B. coli* in gum tragacanth into the peritoneal cavity. In a few cases subcutaneous injection produced sufficient immunity to prevent death. In unimmunized dogs, death always resulted from such fecal contamination.

IMMUNIZATION OF HORSES TO ERYSIPELAS STREPTOCOCCUS TOXIN. JOHN F. ANDERSON and GEO. F. LEONARD.

Methods of immunizing horses to erysipelas streptococcus toxin was given. It corresponds closely to the method of immunizing against scarlet fever toxin. Two series totalling forty-eight horses treated by the antitoxin so produced were discussed. The results in the main were favorable. Serum sickness occurred in 18 per cent of the cases.

THE INCIDENCE OF VARIOUS SPECIES OF BACTERIA IN SPECIMENS OF SPINAL FLUID FROM CASES OF MENINGITIS. RUTH GILBERT and MARION B. COLEMAN.

In 284 cases of meningitis from the rural districts of New York, tubercle bacilli were found in 167, meningococci in 18, influenza bacilli in 23, pneumococci in 33, streptococci in 35, other bacteria in 8.

SIPHONIC FERMENTATION TUBE FOR THE MORE RAPID ISOLATION OF THE COLON-TYPHOID GROUP OF ORGANISMS. F. B. JONES.

THE AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY

A CONSTITUENT MEMBER OF THE FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY

Annual Meeting, Rochester, N. Y., April 14, 15, 16, 1927

WADE H. BROWN, *President;* E. B. KRUMBHAAR, *Secretary*

MYRTILLIN. F. M. ALLEN and RICHARD WAGNER, Morristown, N. J.

Myrtillin is most conveniently obtained by extracting the green leaves of the myrtle family of plants. It is different chemically and physiologically from any substance heretofore described as affecting carbohydrate metabolism. It produces neither toxic effects nor hypoglycemia. It is effective by oral administration. In normal animals and persons it depresses the hyperglycemia following

administration of dextrose. Totally depancreatized dogs receiving myrtillin are enabled to heal wounds like normal dogs and to live and maintain weight for several weeks. They still have hyperglycemia and glycosuria, but less than without myrtillin. Dogs partially depancreatized to such a degree that they would ordinarily have extremely severe diabetes, maintain good health without glycosuria under the influence of myrtillin. Hypothetically, myrtillin is regarded as one of the substances participating in carbohydrate metabolism, in all protoplasm. Its action in cases of diabetes in man will be described in a subsequent paper.

EXPERIMENTAL STUDIES ON MENSTRUATION AND OVULATION IN MACACUS RHESUS. GEORGE W. CORNER, University of Rochester.

In young mature females of the monkey, *Pithecus (Macacus) rhesus,* menstruation frequently occurs without ovulation, and is, therefore, not dependent on the presence of a corpus luteum. However, when ovulation occurs, it seems to take place at a definite time, about twelve or fourteen days before the onset of menstruation. Menstruation without ovulation is not preceded by the so-called "premenstrual" changes of the endometrium, which occur only after formation of the corpus luteum. The cause and meaning of menstruation in this species are not at present known. Physicians in a position to obtain human material are urged to gather and study it in the light of these new facts discovered in a related species.

THE OCCURRENCE OF MITOCHONDRIA-RICH AND MITOCHONDRIA-POOR CELLS IN THE THYROID GLAND OF MAN AND ANIMALS. DAVID P. SEECOF, Montefiore Hospital, New York.

In all the animals examined — human, dog, rat, rabbit, cat, guinea-pig, chicken and pigeon — definite alterations in the number, form and distribution of the mitochondria in the thyroid cell occur during hypertrophy and involution of the gland. In certain cells which were found in variable numbers in the glands of the different species of animals and in the same species under different conditions, the mitochondria differed from those in the predominating or chief cells in thickness, in certain staining reactions and in total amounts present. These differences were not in any way dependent on the size of the cell.

From the available data it has not been possible to correlate any of the specific functional activities of the thyroid cell with the variations in the mitochondrial contents seen in the mitochondria-rich, mitochondria-poor and chief cells.

The cells with increased amounts of mitochondrial substance are present in greater numbers in the human gland than in any of the animals examined. In a small series of cases the numbers of the mitochondria-rich cells could not be correlated with the clinical syndromes attributable to thyroid disease, although they were most numerous in glands from older patients and in glands which showed adenomatous changes.

EFFECT OF LARGE DOSES OF IODINE ON PRODUCTION OF HEAT IN RABBITS. DAVID MARINE, MAX DEUTCH and ANNA CIPRA, Montefiore Hospital, N. Y.

Experiments were carried out on eighteen rabbits to determine whether the metabolism-lowering effects of the sudden administration of large doses of iodine were due to pressure retention brought about by the well known involuting effects of iodine on thyroid hyperplasias or were specific reactions in cases of exophthalmic goiter.

Our material was unfavorable in that none of the thyroids was hyperplastic as determined by control biopsies. With two exceptions, 0.075 cc. of a compound solution of iodine or 25 mg. of potassium iodide was given daily for three consecutive days, and the metabolism was studied daily for two weeks. A significant drop in heat production was obtained in five rabbits, no change in eleven, and in two which received 0.75 cc. of compound solution of iodine daily for eight days a slight rise was observed, beginning at the fifth day.

The experiments failed to answer the question whether a relationship existed between the fall in production of heat and the degree of thyroid hyperplasia, because no definitely hyperplastic glands were included in the series.

They establish the fact that a drop in heat production following the sudden administration of large doses of iodine is specific for exophthalmic goiter neither for rabbits nor for man.

THE EFFECT OF HISTAMINE IN SUBLETHAL SUPRARENAL INSUFFICIENCY. W. J. M. SCOTT, University of Rochester, N. Y.

Suprarenalectomized rats have a greatly diminished minimum lethal dose for histamine. Ten mg. per hundred grams of weight injected intraperitoneally in the second week after operation regularly kills doubly suprarenalectomized rats and none of the controls on which operations had been performed. This susceptibility to histamine is proposed as a quantitative criterion in studying sublethal suprarenal deficiency. Rats with suprarenal deficiency have a latent abnormality which manifests itself by mucosal hemorrhages after the toxic effect of histamine, killed bacteria or a lethal suprarenal insufficiency.

DISCUSSION

DAVID MARINE: We have confirmed this increased susceptibility to histamine in suprarenal deficiency.

F. C. MANN: I should like to call attention to the importance of changes in the viscosity of the blood, and also to the fatal effects of even thirty minutes exercise in suprarenal insufficiency.

EFFECT OF FOLLICULAR EXTRACT ON THE GENERATIVE ORGANS OF HYSTERECTOMIZED GUINEA-PIGS. LEO LOEB and W. B. KOUNTZ, Washington University School of Medicine.

In former investigations we have shown that the corpus luteum has three functions: (1) it inhibits ovulation and regulates the periodicity of the sexual cycle; (2) it sensitizes the uterine mucosa so that it is able to produce maternal placenta and induces slight preliminary proliferation in the mucosa; (3) according to Ancel and Bouin, our own and Hammond's observations, it induces processes of growth in the mammary gland. We concluded, furthermore, that, independently of the corpus luteum, the maturing follicles cause the changes taking place during estrus and, in addition, cause proliferation of the mammary gland. Therefore we divided (1917) the sexual cycle into two successive phases, namely, (1) the follicular and (2) the lutein phase. On the bases of their investigations concerning the action of the follicular fluid, Frank, Allen and others concluded that the follicular fluid contains the only ovarian hormone and that the corpus luteum serves merely as a depository of the follicular hormone.

Our present investigations, in which we injected follicular extract into guinea-pigs and made a thorough microscopic study of the generative organs of a large series of animals, fully confirm our previous conclusions as to the functions

of the corpus luteum and its hormones and as to the existence of the follicular and lutein phases in the cycle. In addition, they confirm our previous observations, which indicated that hysterectomy in guinea-pigs preserves the corpus luteum for a long time. Hysterectomy thus produces effects similar to pregnancy. In hysterectomized guinea-pigs, the effects of the corpus luteum can therefore be especially well demonstrated — in particular its antagonism to the action of the follicular hormone and its effects on the mammary gland. We observed that the action of the follicular hormone in the hysterectomized guinea-pig is similar to that in the pregnant animal, owing to the long persistence and larger size of the corpus luteum in both conditions.

CHRONIC DUODENAL ULCER IN ANIMALS WITH ECK FISTULAS ON CERTAIN DIETS. JESSE L. BOLLMAN and FRANK C. MANN, Rochester, Minn.

A high incidence of chronic duodenal ulcer in our animals with Eck fistulas has been noted for about two years. Grossly and microscopically, these ulcers appear similar to the chronic peptic ulcer in man. In most instances perforation of the ulcer was found to be the cause of death. Since we had not previously observed ulcer in many animals with Eck fistulas, we were inclined to credit a change in diet which was instituted at that time, namely, the addition of cooked cereals and scraps of bone, as the cause of the ulcer. The emptying time of the stomach is greatly prolonged by this diet. The removal of the cereal mixture from the diet appears to have eliminated the occurrence of ulcer. The ulcers occurred only in animals with Eck fistula, in animals with biliary obstruction and in a few animals following removal of part of the liver. Many other animals on this same diet for similar periods did not develop ulcer.

REACTION IN THE LUNGS TO FATS AND OILS. HENRY PINKERTON, Peter Bent Brigham Hospital, Boston.

Cod liver oil fed to infants by the drop method and mineral oils applied in the nose may go into the lungs in large amounts. When investigated experimentally, it was found that vegetable oils apparently excite little or no reaction on the part of the ciliated epithelium, and may even stay in the lungs several months and not cause phagocytosis. Mineral oil is next in order of blandness. It is carried to adjacent lymph nodes by phagocytes. Animal oils are taken up and are decomposed rapidly. There may be extensive fibrosis. This method is well adapted to the study of phagocytosis. Some of the strange forms found are perhaps due to chemical decomposition.

FURTHER STUDIES OF THE PATHOLOGY OF DEFICIENCY IN FAT-SOLUBLE A. S. B. WOLBACH and PERCY R. HOWE, of Harvard Medical School.

A deficiency in fat-soluble has a specific effect — the epithelium becomes largely keratinized. We now learn that epithelial changes are due chiefly to new epithelium arising from small foci, not to a transformation of old epithelium. With a return to normal diet, there is a rapid return to normal epithelium, with a marked surrounding cellular infiltration. Attempts are now under way to see how far the epithelial proliferation could be carried, by adding tar effects and other preparations. Professor Saiki, of the Imperial Metabolic Institute of Tokyo, has obtained even more marked results; in one case a pulmonary metastasis occurred. The guinea-pig seems to be a more suitable animal than the rat, results being obtained in three weeks, which in the rat would have taken three months.

DISCUSSION

DR. PAPPENHEIMER: Similar results have been obtained with chopped hair; it is possible that shed hair may be a factor here also.

HYPOGLYCEMIA FOLLOWING INTRAVENOUS INJECTIONS OF PARATYPHOID B FILTRATE IN DEPANCREATIZED DOGS. MAUD L. MENTEN and HAROLD A. KIPP.

Injections of paratyphoid B filtrate into veins of normal dogs is followed by an immediate rise in blood dextrose, which reaches a maximum of from 160 to 250 mg. per hundred cubic centimeters of blood in from one to two hours, with a return to normal in from four to eight hours. The change in the inorganic phosphates closely follows that of the dextrose, the maximum increase of from 7 to 10 mg. per cubic centimeter being coincident with the greatest hyperglycemia.

Injections of similar amounts of the same filtrate into depancreatized dogs in which diabetes had been controlled by daily injections of insulin, from six to ten days after the operation, caused a gradual diminution in the dextrose content and produced a fatal hypoglycemia of 50 to 40 mg. per hundred cubic centimeters in from nine to fifteen hours. During this period the inorganic phosphates showed a progressive rise from an initial value of 6 mg. to 12 to 15 mg. at death.

Injections made from ten to twenty-one days after the pancreatectomy caused a decrease, reaching from 150 to 160 mg. in from three to five hours, with a corresponding rise of the phosphates to 9 to 10 mg. during the same period. Following this there was a gradual rise of the dextrose with a corresponding diminution in the phosphates until the original value of both was reached. This required from eight to ten hours.

In dogs infected with staphylococcus or streptococcus, the hypoglycemia induced by the injected filtrate was profoundly modified. The changes in the phosphates persisted, while the hypoglycemia was either lessened or entirely lacking, depending on the intensity of the infection. Removal of the pancreas exerts a profound effect on the reaction in the blood induced by intravenous injections of paratyphoid B. Since studies have been made in the twenty-four dogs operated on only up to twenty-one days after operation, it is not possible to exclude completely shock as a possible explanation of the phenomena observed, although similar curves obtained at ten and twenty-one days after operation in the same dog strongly suggest that some other unknown factor is responsible.

PREPARATION AND PROPERTIES OF MYRTILLIN. RICHARD I. WAGNER, Physiatric Institute, Morristown, N. J.

Myrtillin shows a marked effect in depressing alimentary glycosuria in normal dogs. An active principle has been found in various plants and even micro-organisms, which plays an important part physiologically in carbohydrate metabolism. Some details of preparation and properties were given.

RESULTS FROM THE USE OF THE BLOOD CLOT METHOD OF IMMUNIZATION. JOHN F. ANDERSON and GEORGE F. LEONARD, New Brunswick, N. J.

The use of the blood clot method described by Zinsser and Grinnell for the immunization of horses has been found to be of great advantage in the preparation of scarlet fever antitoxin, erysipelas antitoxin and antitoxins against

other strains of streptococci. It is believed that the method offers advantages over other methods of immunization in that a shorter period of immunization is required, and a higher potency of the antitoxin is obtained.

KINETICS OF EXOSMOSIS OF WATER FROM LIVING CELLS. MORTON MCCUTCHEON and BALDWIN LUCKE, University of Pennsylvania, and Marine Biological Laboratory, Woods Hole, Mass.

In a previous communication the authors presented data on the rate with which water enters the living cell (the unfertilized egg of the sea urchin) under the driving force of osmotic pressure. The present paper is concerned with the reverse process — exosmosis of water.

The response of cells to changes in osmotic pressure of the medium is believed to be an important adaptive mechanism. When the cell is placed in sea water diluted with distilled water — hypotonic solution — the cell swells, due to endosmosis of water, while, conversely, the cell shrinks in hypertonic solutions, due to exosmosis. The rate of swelling or shrinking can be determined by measuring the cells under the microscope at minute intervals. Since the cell is spherical, its volume can readily be calculated from its observed diameter, and thus the amount of water which enters or leaves the cell in a given time can be determined. It was found that in exosmosis as well as in endosmosis of water, the rate of flow at any instant is proportional to the amount of water that must still pass the cell membrane before the cell reaches osmotic equilibrium with its surroundings. Expressed mathematically, we have $\frac{dx}{dt} = (a\text{-}x)$ in which $\frac{dx}{dt}$ is the rate of osmosis, a is the total amount of water passing the membrane, x is the amount which has already passed at a time t, and k is the velocity constant. In order to determine whether there is any difference in rate between endosmosis and exosmosis, cells were placed in 60 per cent sea water (that is, sea water, 60 parts; distilled water, 40 parts) and the values of k determined for several temperatures. Then the cells were put back in 100 per cent sea water (that is, sea water of full strength), and the constants for shrinking were determined at the same temperature. Under these conditions it was found that k had a much greater value in shrinking than in swelling, at corresponding temperatures.

Subsequent experiments showed that this difference was due not to any essential dissimilarity between exosmosis and endosmosis, but to the fact that the two processes had occurred in different concentrations of the medium — endosmosis in 60 per cent sea water, exosmosis in 100 per cent. When the two processes took place in solutions of the same osmotic pressure, practically the same values of k were obtained.

This experiment was performed by first obtaining values of k for swelling in 60 per cent solution. Another lot of eggs were then allowed to swell in a more hypotonic solution — 50 per cent — and after swelling was complete, they were placed in 60 per cent sea water, in which they shrank. The velocity constants for shrinking now agreed with those for swelling at the several temperatures. It follows from this and similar experiments that exosmosis and endosmosis are affected in the same way by temperature. The temperature coefficient in each case is high. As the result of these experiments, it is believed that there is no difference in the mechanism of exosmosis and endosmosis of water, except that the driving force of osmotic pressure is exerted in opposite directions in the two cases.

EFFECT OF SALT CONCENTRATION OF THE MEDIUM ON THE RATE OF OSMOSIS OF WATER THROUGH THE MEMBRANE OF LIVING CELLS. BALDWIN LUCKE and MORTON MCCUTCHEON, University of Pennsylvania, and the Marine Biological Laboratory, Woods Hole, Mass.

Of the external factors that affect the rate of osmosis in living cells, temperature has been discussed previously. The second factor, which is the subject of this communication, is the osmotic pressure of the medium. When the unfertilized egg of the sea urchin is allowed to swell in hypotonic sea water or to shrink in hypertonic, the rate has been found to be proportional to the amount of water which will pass the membrane before the cells reach osmotic equilibrium with the medium; or, $\frac{dx}{dt} = k\ (a\text{-}x)$, when a is the total volume of water entering or leaving the cell, x the amount that has already passed the membrane at time t, and k is the velocity. The value of k was found to decrease as the osmotic pressure of the medium is lowered; that is, the lower the osmotic pressure of the medium, the longer it takes the cell to swell halfway from its original volume to its final volume at equilibrium. In order to reach an understanding of this relation, it was necessary to study a wide range of concentrations of the medium — from 20 per cent sea water (20 parts of sea water to 80 parts of distilled water) up to 125 per cent (sea water evaporated to four-fifths of its original volume). In the lower concentration, the velocity constants were determined by swelling experiments, while for higher concentrations the cells were first allowed to swell in dilute solutions and then to shrink in more concentrated solutions, k being determined for shrinking. This procedure was justified by the experiments reported in the preceding abstract, in which it was shown that the velocity constant for swelling and shrinking is the same at a given temperature, provided that the concentration of the medium is the same. When the velocity constants are plotted against the concentration of the medium, an S-shaped curve is obtained. At 15 degrees, k is over ten times as great in 125 per cent sea water as in 20 per cent. This relation points to some factor modifying the ordinary laws of diffusion. It is believed that this factor is a change in permeability of the membrane to water, this permeability being apparently low in dilute solutions and higher in concentrated ones. A hypothesis is offered of the structure of the cell membrane that appears to account for this behavior. It is suggested that diffusion occurs through the pores of a partially hydrated gel which is permeated by the medium and in osmotic equilibrium with it. When the solution is diluted, the gel takes up water from it and swells, so narrowing the pores, while the reverse process occurs when a more concentrated medium is used. The egg of the sea urchin has proved to be an excellent natural osmometer which presents many advantages over the artificial osmometers ordinarily employed. By its use, we have obtained data on rates of osmosis from which deductions can be made on the mechanism of osmosis, on the laws governing diffusion of water and on the nature of cell membranes.

FURTHER OBSERVATIONS IN EXPERIMENTAL NEPHRITIS. J. LOESCH, Morristown, N. J.

In experiments for the production of certain lesions of the kidney associated with hypertension, the difficulty of obtaining frequent blood pressure readings without disturbance of the animals has been overcome by the use of the simple manometer method described by Allen. The other difficulty, limitation of the injury to the kidneys, has been overcome by subjecting the kidneys to repeated ischemia by clamping the renal vessels. In some cases both kidneys were first

transplanted into the skin, in others one kidney was transplanted and later the other was removed. In this way the renal circulation could be cut off by long rubber-covered clamps applied to the renal vessels at any time and without any other appreciable disturbance of the animal. During an interval of at least six months between the preparatory operations and the actual clamping experiments, the animals were kept in good condition on liberal mixed diet, and any animals showing impairment of function in the kidneys were rejected. The ischemia of the kidneys was maintained for periods of ten minutes, increasing gradually up to thirty minutes every third or fourth day. Necrosis was never thus produced, and the various partial functions were surprisingly well preserved until after several clampings a week or two apart.

The chief results may be summarized as follows:

1. Injuries of the kidneys alone by means of ischemia give rise to hypertension, the increase of pressure amounting to from 16 to 46 mm. in dogs with one kidney and to from 36 to 64 mm. in dogs with two kidneys.

2. The increase of blood pressure is caused by: (*a*) changes in the kidneys themselves, and (*b*) by an extrarenal factor, which, however, is secondary to the renal disturbance.

3. The degree of elevation of pressure is governed by the changes in number and caliber of the renal vessels, and also by a functional factor which is demonstrably connected with the salt metabolism.

4. The functional capacity of the kidney is determined largely by the quantity of parenchyma present. Under practically identical conditions of diet and ischemia, the dogs with one kidney die of uremia, while those with two kidneys show only slight elevation of urea in the blood.

5. Microscopically, the kidneys show the effects of irritation in the form of cell proliferations in the capsules and tufts of the glomeruli, and the effects of circulatory disturbance in the form of necrosis with consequent inflammation. Overgrowth of connective tissue and atrophy of the glomeruli leads to a final stage of hyaline degeneration.

6. The small blood vessels show thickening of the walls, up to complete obliteration.

7. The tubules show desquamation, necrosis and flattening of the lining epithelium.

AN EXPERIMENTAL STUDY OF THE ACTION OF LEAD ON THE KIDNEY. SLAVKO PEJICH, University of Michigan.

ANATOMIC CHANGES IN THE KIDNEYS OF RABBITS FOLLOWING ADMINISTRATION OF MERBAPHEN AND SODIUM MERCURISALICYLALLYLAMIDOACETATE. STANLEY P. REIMANN and F. WINKELMANN, Lankenau Hospital, Philadelphia.

Merbaphen, first used as an antisyphilitic measure, was found to possess marked diuretic properties. Certain disadvantages led to the production of sodium mercurisalicylallylamidoacetate, which contains approximately the same amount of mercury, 35 per cent, but is apparently less toxic. The chief mode of action of both is a water and salt diuresis, both probably caused by action on the tissues and the kidneys. Since both drugs contain mercury, they must be administered with caution; the field of usefulness is in cardiac edema with minor changes in the kidneys. Chemical studies can be found in the literature. Since no patient with severe cardiac decompensation and edema has normal kidneys, the drugs sometimes do considerable damage. Apparently, instead of being immediately excreted, they are retained and produce salivation and bloody

diarrhea. Rapid death has occurred in several instances. Since all of this is in the literature, and since we have had several experiences with salivation and diarrhea, but not of death, we think it wise to emphasize the toxicity of sodium mercurisalicylallylamidoacetate. Given to rabbits, it produces a typical mercurial tubular nephritis with necrosis, disintegration and calcification in the tubules, especially the convoluted tubules and the ascending limbs of Henle's loop. The changes begin on the second or third day, and rabbits were killed at daily intervals until they died from an overdose in from eight to ten days, or were killed at the end of that time to study the changes. Primary functional examinations determined the intactness of the kidneys of the animals, and a larger dose by about three to four times, (1 cc. is the dose for a human being) was given on the assumption that those individuals who receive 1 cc. of the solution as prepared commercially, in reality receive considerably more, because of the damage already present in their kidneys. The drug must be administered with great caution. In well selected cases it has an amazing influence on diuresis and thus on the relief of edema.

EXPERIMENTAL EDEMA AS AN AID TO MICROSCOPIC STUDIES. SAMUEL R. HAYTHORN, University of Pittsburgh.

Several methods of superimposing edema and serous exudates on other experimental lesions are reported. With the additional aid of special stains, several interesting observations were made possible by these methods on phagocytosis of pigments, early tubercles, encapsulation of tubercles and formation of giant cells.

CHOLESTEROL CHANGES IN CHRONIC NEPHRITIS WITH AND WITHOUT EDEMA. FRANCIS D. MURPHY, Milwaukee.

The elevation of the blood cholesterol in certain types of chronic nephritis has been the subject of investigation for the past fifteen years. In so-called chronic parenchymatous nephritis and especially in the type known as pure lipoid nephrosis, a hypercholesterolemia is common (Strauss, Stepp, Fahr, Kollert, Daniels and others). Concerning the existence of the doubly refracting lipoids in the urine and tubular epithelium of patients with nephritis the information is less positive, although in 1902, Kaiserling and Orgler demonstrated doubly refracting lipoids in the urine in so-called myelin kidney. Aschoff and Adami established the fact that this doubly refracting substance was cholesterol ester. Experimentally Chalatow, Weltmann, Biach and Gench and others were able to produce a hypercholesterolemia by feeding cholesterol to rabbits, but infiltration of tubular cells developed only after the cells had been previously injured. Dewey produced changes in kidneys in rabbits similar to those of the large white kidney in man by injecting cholesterol intraperitoneally and intravenously. She found a definite selective localization of the lipoids in the tubules. Lowenthal found a parallelism between the hypercholesterolemia and the degree of edema. By feeding rabbits cholesterol he produced a hypercholesterolemia and a lesion similar to lipoid nephrosis in man. Edema was not produced, and he did not determine whether hydremia existed. Twenty-five patients with chronic glomerular nephritis were studied; fourteen were edematous, and eleven were not. The blood cholesterol was determined, the urine examined for doubly refracting lipoids, as was the tissue of the kidney in those patients who came to autopsy (fourteen of the seventeen who died). No case of pure lipoid nephrosis is included; all were types of chronic diffuse glomerular nephritis. The patients with edema frequently, but not invariably, had hypercholesterolemia and usually doubly refracting lipoids in the urinary

sediment. Without exception the patients with edema (of renal type) examined at post mortem had, in addition to diseased tubular epithelial cells, deposits of doubly refracting lipoids in the cells. The patients that were free from edema usually had no hypercholesterolemia or doubly refracting lipoids in the urine. After death in such cases, disease was always present in the tubular cells, but no doubly refracting lipoids were found in the epithelium.

While the substances referred to as doubly refracting lipoids also took the usual fat stains, they are considered cholesterol esters because of their double refracting quality. It is known that there are other tests useful in differentiating cholesterol esters from neutral fats, and the complete histochemical analysis of the lipoid substances referred to will be the subject of a future report.

An analysis of the cases indicates that the blood cholesterol is usually normal in the edema-free patients, while in patients with chronic nephritis and edema, hypercholesterolemia is common.

One is led to conclude that it is neither the elevation of the blood cholesterol alone, nor the diseased tubular epithelial cells alone, that influences the mechanism of the production of edema, but the combination of diseased tubular cells and the presence in these cells of cholesterol esters, is the factor which seems connected with production of edema.

TULAREMIA: COMPARISON OF LESIONS IN MAN AND ANIMALS. G. R. CALLENDER, Washington, D. C.

The animals in which the microscopic changes caused by artificial infection with *Bacillus tularense* have been studied are the rabbit, guinea-pig, rat, mouse and opossum. The lesions in naturally infected animals have not been described microscopically, though the disease was first recognized in the ground squirrel of California and has been found most prevalent in wild rabbits. The lesions in man have been described from one case by Permar and briefly described by other authors. The earliest lesions in man are of the focal necrosis type, and relatively little tissue resistance is present. A cellular resistance to the invasion is quickly developed, however. It is characterized by proliferation of endothelial cells, the formation of multinucleated syncytial masses, fibroblastic increase and lymphatic infiltration occurring in the order named. The longer the duration of the disease, the more rapidly do fibroblasts proliferate in an attempt to wall off and obliterate the lesion.

When the focal lesions are disseminated, in man the process is pyemic, affecting particularly the lungs, liver, spleen and lymph nodes. In such cases one finds both early and late lesions, the early ones showing little more than focal necroses with leukocytic infiltration, the older ones more or less fibrosis. While tularemia per se undoubtedly has some mortality, many of the patients die from secondary infectious processes originating in the local lesion or from acute respiratory infection.

The experimental animals so far worked with are much less resistant than man to the progress of the infection. The mouse shows practically no resistance, and the parenchymatous organs, particularly the liver and spleen, are intensely affected. The rat and opossum are somewhat more resistant, as is true of the rabbit and guinea-pig. Lesions in the spleen in the guinea-pig show a fairly close resemblance to the early lesions seen in man.

THE DISSOCIATION OF BACILLUS SUBTILIS. M. H. SOULE, University of Michigan.

From cultures of *Bacillus subtilis* (some of which were from single cell isolations) at least three types of organisms were isolated: the normal or S form, which is equivalent to that first described by Ehrenberg and later by

Cohn, Koch and others; an R or resistant form, which varies morphologically and culturally from the classical type and which has not been found adequately described in the literature, and a P or intermediate form, which varies morphologically and culturally from the S and R types and which has not been previously described. In broth the R strain produced nonmotile filaments, which often attain a length of 200 microns and which rapidly agglutinate with the formation of a flocculent precipitate. The surface colonies on agar are somewhat irregular and flat, with cuneate surfaces which sparkle by oblique transmitted light. Microscopically, these colonies cannot be differentiated from anthrax. This form does not liquefy gelatin as rapidly as does the normal type; the colonies on gelatin are composed of twisted filaments and characterized by edges that are curled under. The P type does not grow in liquid mediums. Many attempts have been made to obtain broth cultures, but to date all efforts have been unsuccessful. To obtain serial cultures from agar plate to agar plate, it is absolutely necessary to use salt solution or distilled water in taking up the material from a colony to get the subcultures. The surface colonies on agar are flat, colorless and practically invisible. Under the low power objective, the colonies have a somewhat coccleate appearance. This form does not liquefy gelatin; the germs occur typically in pairs and are actively motile, and the individual bacilli are lance-shaped.

Biochemically, the S and R forms have been found identical in their reactions. There is no difference in the production of spores by these two forms; spores have not been observed, however, in cultures of the P type.

Large volumes of fluid medium inoculated with the S type result in the production of R forms in proportion to the quantity of medium and the interval of active growth. Washed cells suspended in salt solution or in distilled water do not dissociate, and spores kept under these conditions fix their own correlated vegetative types. The S type may be produced from R strains by inoculating large volumes of fluid medium, but the percentage of S forms obtained from R types is much smaller than the percentage of R forms produced from S strains under the same conditions. The R form thus seems to be the stable form. The S form is more strongly antigenic. Immune serum has a marked dissociating power on its homologous germ and a stabilizing action on the opposite form. By the incorporation of S or R immune serums in fluid medium, R forms can be obtained from S forms, and S from R, respectively. The P type can be isolated from cultures of the R or S type which are undergoing rapid dissociation, and is apparently an intermediate form between the R and the S types, with a marked tendency to dissociate into the R type.

In addition to pure laboratory cultures, recently isolated strains from hay infusions, air, water and milk have been studied. Both the S and R forms have been obtained from the above sources, but the P type has been isolated only from pure cultures undergoing rapid dissociation.

BACTERIAL VARIATION. L. T. WEBSTER, Rockefeller Institute.

OCCURRENCE OF PARALYTIC PHENOMENA IN RABBITS INFECTED WITH TRYPANOSOMA GAMBIENSE. LOUISE PEARCE, Rockefeller Institute.

The experimental infection produced by two strains of *Trypanosoma gambiense* isolated in November, 1925, differs in several important respects from that commonly observed. In the first place, the successful transmission of the organisms from the patients to laboratory animals and their maintenance by serial passage was accomplished only by the use of the rabbit and the intra-

testicular route of inoculation. Second, the virulence of the strains is usually low. This is shown by the greatly prolonged incubation period — in one instance sixteen months — and furthermore, by the extended duration of life. A number of rabbits have lived from thirteen to eighteen months after inoculation. The inflammatory lesions of the skin and mucous membranes so frequently seen in trypanosomiasis of the rabbit are uncommon with these strains.

The most striking feature of the infection is the frequent occurrence of paralysis of the hind quarters; it has developed in 70 per cent of the animals. The condition begins, on an average, six months after inoculation, with weakness of one or both hind legs and may progress to complete incapacity of movement. In pronounced cases the knee and, to a less extent, the hip joints become extremely loose; the leg muscles may show more or less wasting and flaccidity, and the knee jerks cannot be elicited. Superficial ulcerations of the skin over the buttocks and about the anal region have eventually occurred in certain instances. Incontinence of urine has occasionally been observed, and at autopsy, marked distension of the bladder with retention of urine is not infrequently seen. It is important to note that this paralytic condition is not associated with the terminal stages of the infection, but that it occurs and progresses while the general physical state of the animal is excellent.

Histologically, a degeneration of the posterior columns of the spinal cord has been regularly demonstrated by the use of the Herxheimer and Spielmeyer stains, and it is apparently most marked in the lumbar and sacral regions. In some cases, degenerations of the lateral and anterior columns are also seen. There is a small round cell infiltration of the posterior ganglia and nerve roots which tends toward a perivascular arrangement, the number of ganglion cells appears to be reduced, and varying degrees of a subacute or chronic inflammation of the meninges (cord and ganglia) have been observed.

The available evidence indicates that the production of lesions of the central nervous system by these two strains of *Tr. gambiense* is due to their low virulence.

FURTHER OBSERVATIONS IN NONSPECIFIC IMMUNITY. PAUL F. CLARK, University of Wisconsin.

THE EFFECT OF DEEP ROENTGEN-RAY IRRADIATION ON THE CARDIAC CONDUCTION APPARATUS. F. W. HARTMAN, Ford Hospital, Detroit.

MUSCLE HEMOGLOBIN IN HUMAN MATERIAL AT AUTOPSY. W. W. WOODRUFF, University of Rochester.

A method is outlined for the extraction of muscle hemoglobin from human autopsy material which is comparatively free from blood hemoglobin. It is believed that the values found are accurate within from 5 to 10 per cent. The actual values varied from 400 to 1,100 mg. of muscle hemoglobin per hundred grams of muscle. There was no apparent relationship to age.

BLOOD HEMOGLOBIN PRODUCTION AND CONSERVATION IN SEVERE EXPERIMENTAL ANEMIA. F. S. ROBSCHEIT-ROBBINS and G. H. WHIPPLE, University of Rochester.

The influence of various forms of hemoglobin in the regeneration of blood in severe secondary experimental anemia was studied. Fresh red cells and dried red cells, as well as a blood paste (commercial product) have been added to a basal ration of a bread mixture and fed to anemic dogs. For

intravenous and intraperitoneal administration red cells of dog blood were washed with salt solution and laked with distilled water. The stroma was removed; the cells were made isotonic and injected daily into the jugular vein or peritoneum. Hemoglobin when fed in these forms resulted in a utilization of from 6 to 17 per cent of the amount given. Following both intravenous and intraperitoneal injections from 80 to 90 per cent of the pigment was utilized in the formation of red cells and hemoglobin. The authors believe that these experiments demonstrate the ability of the animal body to conserve and utilize again certain products of hemoglobin in severe secondary experimental anemia.

QUANTITATIVE DETERMINATION OF IRON IN TISSUES. R. P. KENNEDY, University of Rochester.

The small amount of iron that is contained in the animal organism precludes the use of the well known volumetric or gravimetric methods. The method proposed is a simplification of the colorimetric methods hitherto suggested and in summary constitutes digesting about 1 Gm. of material in a mixture of sulphuric and perchloric acids. After diluting to a known volume, an aliquot portion is treated with a concentrated sodium sulphocyanate solution and the resulting ferric sulphocyanate is extracted with amyl alcohol. The alcoholic solution is compared in a colorimeter with a similar solution developed from a known amount of iron. Data are presented showing comparative analyses done on blood solutions by three methods: the oxygen capacity, spectophotometric and iron methods. The average deviation of the iron found from 0.334 per cent (the theoretical percentage of iron in hemoglobin) is 18 per cent. The method is applicable to tissues as a means of studying accurately the distribution of iron in the organism.

DOES SPLENECTOMY INFLUENCE THE CALCIUM CONTENT OF THE BLOOD? E. B. KRUMBHAAR, University of Pennsylvania.

Following a report that splenectomy was followed by a marked decrease in blood calcium, two Airedale bitches, about two years old (full sisters), were splenectomized after complete blood counts and estimations of serum calcium (Clark and Collip's method) had been made. While the usual leukocytosis, thrombocytosis, slight anemia and definitely increased resistance of erythrocytes to hypotonic salt solution was found, no significant changes in either serum calcium or phosphates were found, though a drop in calcium beyond the limits of error of the method was observed. Thus the presplenectomy calcium figures were: Dog. 1, 12.1 mg.; Dog 2, 13.6 mg. One day later: 11.3 and 12.7 mg.; two days: 11.3 and 11.9 mg.; five days, 13 and 12 mg. (both wounds open); fourteen days, 11.8 and 11.5 mg.; twenty-eight days; 12.9 and 12.5 mg.; two months, 11.9 and 12.1 mg.; six months, (summer, fasting twenty-four hours) 9.3 and 9.2 mg.; one year, 10.3 and 11.0 mg.

Book Reviews

AN INTRODUCTION TO THE STUDY OF EXPERIMENTAL MEDICINE. By CLAUDE BERNARD. Translated by Henry Copley Greene, A.M. With an Introduction by Lawrence J. Henderson, Professor of Biological Chemistry, Harvard University. Price, $3. Pp. 226. New York: The Macmillan Company, 1927.

This book was first published in 1865. Claude Bernard was then 52 years of age and had been completely absorbed in the experiments that led to his great discoveries. A severe illness resembling in many features appendicitis, had enforced on him a prolonged period of isolation and physical rest, and during that time he elaborated leisurely his matured thoughts and convictions about the experimental method as applied to physiology and medicine. The book was received with admiration mingled with surprise because of the unexpectedly marvelous art with which the importance of the experimental method was set forth and its rules formulated. The book has been reprinted in French, but this is the first time that it is given a special introduction to a new audience through an English translation. To speculate on the cause of the delay of translation would be interesting, but of little if any use. It may be noted, however, that contemporary discoveries, mainly by Pasteur, for a time at least diverted attention and interest from general experimental medicine to the intensive study by new technical methods of infection, microbes and immunity. Consequently, the appearance of this translation after sixty-two years may be looked on as the outcome of an increasing interest in experimental medicine and as a surer recognition of the fundamental value of the book as a guide and stimulus to the experimental method; or the delay may be regarded as signifying that when all is said, Claude Bernard was at least a half a century ahead of his time.

Lawrence J. Henderson contributes an analytic introduction of special interest; then there is a short but highly significant account of Claude Bernard by his pupil and successor at the Sorbonne, Paul Bert, dated Feb. 12, 1878, hence written shortly after the master's death. The book itself consists of a preface and three parts. The object of the book is practical, namely, to aid in conserving health and in curing disease by placing medicine under the domain of the experimental method. The first part considers experimental reasoning in two chapters: on observation and experiment and on the *a priori* idea and doubt in experimental reasoning. Unfortunately, "no rules can be given for bringing to birth in the brain a correct and fertile idea that may be a sort of intuitive anticipation of successful research. The idea once set forth, we can only explain how to submit it to the definite precepts and precise rules of logic from which no experimenter may depart; but its appearance is wholly spontaneous, and its nature is wholly individual."

"The experimenter puts questions to nature; but as soon as she speaks, he must hold his peace; he must note her answers; hear her out and in every case accept her decision.

"Nothing is accidental, and what seems to us accident is only an unknown fact whose explanation may furnish the occasion for a more or less important discovery."

In the second part, experimentation with living beings is discussed under experimental considerations common to living things and to inorganic bodies and then under considerations peculiar to living bodies. Claude Bernard had

an immovable confidence in the explainability of vital phenomena and proclaimed that the same method whose laws lead to certainty in the sciences of dead matter have equal authority in the sciences of living beings.

"We must therefore, in my opinion, stop differentiating the phenomena of living bodies from those of inorganic bodies, by a distinction based on our ability to know the nature of the former and our inability to know the latter. The truth is that the nature or very essence of phenomena, whether vital or mineral, will always remain unknown."

In the third part, he deals with applications of the experimental method to the study of vital phenomena, presenting examples from his own work in experimental physiologic investigation and experimental physiologic criticism, discussing also investigation and criticism as applied to experimental medicine and philosophic obstacles encountered by experimental medicine.

"Medicine necessarily begins with clinics, since they determine and define the objects of medicine, i. e., the medical problem; but while they are the physician's first study, clinics are not the foundation of scientific medicine; physiology is the foundation of scientific medicine because it must yield the explanation of morbid phenomena by showing their relations to the normal state.

A physician should not hold to anatomical pathology alone, to explain the disease; he starts from observation of the patient and later explains the disease by physiology with the help of pathological anatomy and all the allied sciences used by investigators of biological phenomena."

"I deem it highly important to guide the minds of students early toward experimental science, by making them understand what develops in the laboratories, instead of leaving them to believe that it awaits them in books or in the interpretation of ancient writings."

The author thus gives an honest and successful and illuminating analysis of himself at work. He illustrates the experimental study of vital phenomena by examples from his own work. He describes instances in which the starting point of his experiments was an observation from which he passed by experiment after experiment to new facts and ideas (significance of acid urine in the fasting rabbit, discoveries of fat-splitting action of pancreatic juice, of the achon of curare, of the mechanism of carbon monoxide poisoning), and then his experiments, based on an erroneous hypothesis, that finally led to the discovery of glycogenesis in the liver. "When we meet a fact which contradicts a prevailing theory, we must accept the fact and abandon the theory, even when the theory is supported by great names and generally accepted."

The translation runs smoothly, and the original meaning seems to come out clearly. The style is clear, forceful and direct, and many choice passages occur; for example, "Those who do not know the torment of the unknown cannot have the joy of discovery which is certainly the liveliest that the mind of man can ever feel."

A spirit of honesty, modesty, calm frankness and good sense prevails throughout. The book should be studied by all who are interested in the advancement of medical science. It is one of the most instructive, stimulating and inspiring books that the investigator, young or old, can read. It is the law and the gospel of experimental medicine. It was a happy idea indeed that led to this translation because it will have a far-reaching influence now that medicine in our country is definitely entering on the experimental stage.

"Medicine is destined, then, to get away from empiricism little by little; like all other sciences, it will get away by the scientific method. This

deep conviction sustains and guides my scientific life. I am deaf to the physicians who ask us to explain measles and scarlet fever experimentally, and who believe they can find in them an argument against using the experimental method. These discouraging, negative objections generally come from systematic or lazy minds that prefer resting on their systems or sleeping in the dark, to working and making an effort to get away. The different branches of physico-chemical science were elucidated only gradually, step by step, by the experimental method, and they still have today obscure parts which we are studying with the help of the same method. In spite of all the obstacles that it meets, medicine will follow the same course; it will follow it necessarily. In extolling the introduction of the experimental method into medicine, I am therefore only trying to guide men's minds toward a goal that science is instinctively and unconsciously pursuing—a goal that it will more quickly and certainly reach if it can succeed in seeing it clearly. Time will then do the rest. Of course, we shall not see scientific medicine blossoming in our day, but that is man's lot; those who sow and laboriously cultivate the field of science are not also destined to reap the harvest."

DIE MORPHOLOGIE DER MISSBILDUNGEN DES MENSCHEN UND DER TIERE. Ein Hand- und Lehrbuch für Morphologen, Physiologen, Praktische Aerzte und Studierende, unter Mitwirkung zahlreicher Fachgenossen, begründet von Weil and Prof. Dr. Ernst Schwalbe. Herausgegeben von Dr. G. B. Gruber, O. Oe Professor der Pathologischen Anatomie an der Universität Innsbruck. II. Teil: Die Einzelmissbildungen XII. Lieferung, 3. Abteilung, 1.-3. Kapitel: Die Missbildungen der Muskelsystems (ausschliesslich des Zwerchfells) von Dr. A. Binder, Pforzheim. Die Missbildungen des Zwerchfells, von Prof. Dr. G. B. Gruber, Innsbruck. Dis Missbildungen der Harnorgane, von Prof. Dr. G. B. Gruber, Innsbruck, mit einem Bildniss und einem Einleitenden Gedenkwort an Ernst Schwalbe von Geh. Prof. Dr. Paul Ernst, Heidelberg, mit 1 Titelbild und 252 Abbildungen im Text. Paper. Price, 20 marks. Pp. 374. Jena: Gustav Fischer, 1927.

In the chapter on "Monstrosities and Abnormalities" in the late J. George Adami's "Principles of Pathology" there is the following statement: "There is at the present time in the process of publication what promises to be the leading work upon the subject, judging from the two sections that have thus far appeared, viz., Schwalbe's Morphologie der Missbildungen (Jena, Fischer, 1906 and 1907)." Prof. Adami's expectations have been amply fulfilled, and Schwalbe's great work merits a place in every medical reference library. The work is appearing in sections, written by various authors. The most important subjects covered up to the present time are: general teratology, deduplications, external malformations; malformations of the nervous system, of the female genitalia, of the ear, skin, respiratory structures, heart, great vessels, teeth, head, locomotor system; tissue malformation (neoplastic-like malformations) and postfetal developmental disturbances. The present section deals with malformations of the muscles (by A. Binder); the malformations of the diaphragm (by B. Gruber), and the malformations of the urinary system (by B. Gruber).

The present section also contains a memoir and portrait of the late Prof. Ernst Schnable, written by Prof. Paul Ernst. The subjects discussed are treated in considerable detail, and are well illustrated. There is a full bibliography, and many references are made to recent English and American literature.

The reviewer was particularly interested in the chapter on the diaphragm (pp. 81 to 156). This important muscle has, until the present time, scarcely

received the attention merited. The scope of the work in general may be indicated by citing the subject matter covered in this chapter: normal development, normal anatomy, variations, comparative anatomy, disturbances of the anlage and closure (partial defects), herniation of the diaphragm, diverticulation, eventration and dystopsia of the diaphragm. There are 200 references to this chapter, and 52 illustrations.

Schwalbe's work is just what its title indicates "a Handbook for Morphologists, physiologists, practising physicians and students." It is probably the best reference book on this subject.

SOCIAL FACTORS IN MEDICAL PROGRESS. By BERNHARD J. STERN, PH.D. Price, $2.25. Pp. 136. New York: Columbia University Press, 1927.

How and why are innovations in medicine resisted? To what extent are discoveries inevitable or dependent on the individual work of gifted persons? These are the main questions discussed in this book by a student of sociology with special interest in the dynamics of cultural progress. After a general discussion of the factors — psychologic, cultural, mechanical and personal — that retard the diffusion of innovations and of conservatism as it operates in medicine, the author presents brief reviews of the opposition to dissection, to Harvey's discovery of the circulation of the blood, to Auenbrugger's method of percussion, to vaccination, to the contagious theory of puerperal fever as advanced by Holmes and by Semmelweis, to the discoveries of Pasteur and to antisepsis and asepsis. The causes of opposition to these specific innovations are analyzed critically, and the rôle of the various factors in the opposition is evaluated in each instance. The second part deals with the nature of medical progress, and here the emphasis is placed on the dependence of a discovery on the existing knowledge. "At approximately the same time men make the same discoveries and inventions in medicine independently of one another, because the existing culture contains the elements necessary for the invention." To illustrate this statement there is appended a list, covering several pages, of multiple more or less simultaneous discoveries and innovations in medicine. There are several errors in this list, particularly in the spelling of proper names. The book, though brief and rather sketchy, is interesting and well worth reading.

Books Received

ALLGEMEINE UND EXPERIMENTELLE PATHOLOGIE. Nach Vorlesungen für Studierende und Ärzte Von Dr. Hermann Pfeiffer o.ö. Professor und Vorstand der Lehrkanzel für allgemeine und experimentelle Pathologie an der Universität Graz. Zweite, vermehrte und verbesserte Auflage. Mit 56 teils mehrfarbigen Abbildungen im Text und 8 mehr-farbigen Tafeln. Pp. 649. Price, 22.50 marks. Berlin: Urban & Schwarzenberg, 1927.

DENGUE: Its History, Epidemiology, Mechanism of Transimssion, Etiology, Clinical Manifestations, Immunity, and Prevention. By. J. F. Siler, Milton W. Hall and A. Parker Hitchens. Monograph 20. Paper. Pp. 476, with 8 plates and 97 text figures. Price, $3. Manila Bureau of Printing, 1926.

THE PRINCIPLES OF PATHOLOGY. By Charles Powell White, M.D., F.R.C.S., Honorary Lecturer in Pathology and Director of the Helen Swindells Laboratory in the University of Manchester. Pp. 279. Price, $6. Manchester: University Press. London, New York, etc.: Longmans, Green & Co., Ltd., 1927.

BONE SARCOMA THE PRIMARY MALIGNANT TUMORS OF BONE AND THE GIANT CELL TUMOR. By Anatole Kolodny, Ph.D., M.D., Department of Surgery, State University of Iowa. Pp. 214. Authorized by the American College of Surgeons. Chicago: The Surgical Publishing Company, 1927.

LA VACCINATION PRÉVENTIVE CONTRE LA TUBERCULOSE. Par le "BCG" A. Calmette, Sous-Directeur de L'Institut Pasteur. Avec la Collaboration de C. Guérin, A. Boquet et L. Nègre. Pp. 250. Price, 22 francs. Paris: Masson et Cie, 1927.

KOLLOIDCHEMIE DER WASSERBINDUNG. Eine kritische und experimentelle Untersuchung der Wasserbindung in Kolloiden und ihrer Beziehungen zu den Problemen der Wasserbindung in Physiologie, Medizin und Technik, von Martin H. Fischer Doktor der Medizin und Pharmazie, Eichberg-Professor der Physiologie an der Universität Cincinnati Zweite erweiterte, von Verfasser durchgesehene deutsche Ausgabe Neue Uebersetzung der dritten amerikanischen Auflage von Dr. Katharina Popp. Band 1 Wasserbindung in Odemen, Mit 142 Abbildungen. Pp. 368. Dresden und Leipzig: Verlag von Theodor Steinkopff, 1927.

PUBLICATIONS OF THE SOUTH AFRICAN INSTITUTE FOR MEDICAL RESEARCH. No. XIX. Contributions to the Study of Miners' Phthisis. By A. Mavrogordato, M.A., M.R.C.S., L.R.C.P., Research Fellow in Industrial Hygiene, South African Institute for Medical Research. Pp. 83. Price, 5 shillings. Johannesburg: The South African Institute for Medical Research, 1926.

HYPOTENSION. By Alfred Friedlander, College of Medicine, University of Cincinnati. Pp. 216. Price, $2.50. Baltimore: Williams & Wilkins Company, 1927.

LES MICROBES. P.-G. Charpentier Professeur à L'Ecole de Médecine de Dijon, Directeur de l'Institut d'Hygiène et de Bactériologie. Pp. 77; 59 plates with 130 illustrations in heliogravure. Price, 16.50 francs. Paris: Rieder.